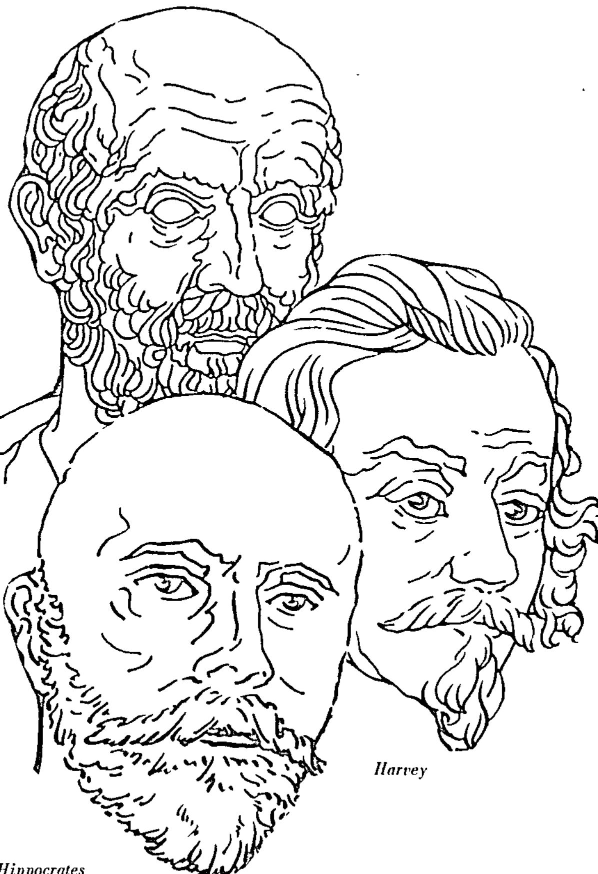


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VOLUME 1

NORMAL HEART AND VESSELS

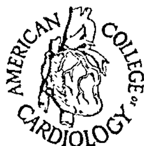
CARDIOLOGY

An Encyclopedia of the Cardiovascular System

SPONSORED BY THE AMERICAN COLLEGE OF CARDIOLOGY

EDITED BY ALDO A. LUISADA, *M.D.*

FOREWORD BY ASHTON GRAYBIEL, *M.D.*



THE BLAKISTON DIVISION

McGRAW-HILL BOOK COMPANY, INC.

NEW YORK TORONTO LONDON



H. De Bellis, M.D.

Cardiology VOLUME 1: *Normal Heart and Vessels*

Library of Congress Catalog Card Number: 58-11165

This work was made possible by generous grants from

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Foreword

This work is at once a landmark in clinical cardiology and an indication of the Golden Age of Medicine in which we now live. Because wondrous things have become commonplace, we can appreciate this age only in retrospect. From rude beginnings it is possible to trace, over the centuries of recorded history, the gradual refinement in skills, the slow accumulation of factual knowledge, and the emergence of a scientific discipline so essential to success in the walks of science. Progress, painfully slow and often faltering till late in the nineteenth century, then began to accelerate at an ever-increasing rate. Within the memory of some now living, individual triumphs in scattered departments of science combined in one mighty triumphant flourish to usher in the modern era. Epidemics, once the scourge of man, were abolished; certain diseases, once relentless in their course, were controlled; old age, once a rarity, became the rule. It is unlikely that within a comparable period of time man will ever again repeat the stupendous feat of doubling his span of life.

Cardiologists, while sharing in these triumphs, saw heart disease assume the lead as a cause of death in many countries Thus, although gratified by the increased longevity of man, we are nevertheless challenged by the disclosure that the cardiovascular system is now the weakest strand in the thread of life. Indeed, its relative importance in the lives of men appears destined to increase, for there is nothing in sight pointing to a major break-through in the prevention of heart disease in old age

In sponsoring this encyclopedia, the American College of Cardiology, dedicated to the continuing education of its membership, is simply fulfilling one of its obligations. That this particular obligation weighed more heavily on the minds of some of its officers than on others raised the question of the relative merits of different methods of postgraduate education. We cannot here record the deliberations which finally led to approval of this undertaking, but they reflected the need for putting on record the widening horizons of our knowledge of cardiovascular disease.

That the presentation of information concerning the heart and circulation requires four volumes involving upwards of 250 authors has important implications It is evidence that narrowing of interest and progress go hand in hand, and that subdivision within the field of cardiology is well established But this subdivision, so essential for progress, must be reconstituted for those whose clinical responsibilities cover a broad area In effect this encyclopedia represents such a reconstitution It contains authoritative information abstracted from an immense mass of medical literature which could not be reviewed effectively by an individual. The organization of this material is based on a logical framework

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which constitutes a resynthesis of the important elements in the field of cardiology.

In using this encyclopedia, the physician must let go of his inclination to be taught, and cultivate the art of selecting new items of information and fitting them into a frame of reference dictated by his needs. This method does require *a capacity for mental independence and is effective only in so far as this is ex*hibited by those for whom the encyclopedia is intended. Admittedly a work of this sort represents a form of communication in which there is much redundancy. At what point will the evil of redundancy equal or exceed the good contained in the message? Herein lies a very real problem with which we should be concerned in the future.

It is noteworthy that in the compilation of this work we are more dependent upon an editor than upon an author. The choice of Dr. Luisada to edit the work has been fortunate. He has exhibited not only a natural talent for this task but also the quality of persevering in the face of difficulties. To him alone belongs the credit for bringing the encyclopedia to fruition. The present handbook must be regarded as a monument to his genius.

ASHTON GRAYBIEL

Preface

This work was started as a result of a bold and far-sighted initiative of Dr. Ashton Graybiel, then president of the American College of Cardiology.

The task of editing an encyclopedia of cardiology represents a challenge which is both appealing and frightening.

Among the multitude of books of cardiology which have been published in the last 20 years, the majority belongs to the type of the medium-sized, monographic textbook written by a single author. A few have been written in collaboration by several authors. These, however, do not attempt to be complete and are, moreover, too unsystematic to be helpful. Being of the "fixed-volume" type, they are soon outdated and, therefore, forgotten.

In ancient Greece, *encyclopaedia* meant "instruction in the whole circle, or complete system of learning." In a more restricted sense, encyclopedia means "a system or classification of various branches of knowledge; a subject on which many books have been published." While many encyclopedias of the past have been of the "alphabetical type" (each word to be explained is listed in alphabetical order), others have tried to reconcile system with completeness. Thus, even in the early editions of the *Encyclopaedia Britannica*, the various sciences and arts (such as anatomy or surgery) were "digested into distinct treatises or systems." On the other hand, technical terms were explained in alphabetical order. Older encyclopedias, like Plinius's *Natural History* of the year 77 A.D. (37 books with 2,493 chapters) or *Yung-Lo Ta Tien*, the Chinese encyclopedia of 1403 A.D (11,095 volumes prepared in four years by over 2,000 scholars), were developed according to system. The latter even included well-known books reproduced without change.

In the opinion of the editor, a modern encyclopedia of cardiology *ought to* have the following characteristics: (1) It should encompass all available knowledge on the heart and vessels, including history, embryology, anatomy, physiology, physical and technical methods of examination, bacteriology and pathology, clinical sciences, surgery, pharmacology and therapy, rehabilitation, and the various "allied fields." (2) It should present them in a systematic order, thus permitting easy consultation (3) It should be of the loose-leaf type, in order to keep abreast of medical progress. It is then possible that some of the readers may prefer to call this a *treatise*.

The principle of extending the work to all kinds of knowledge in the cardiovascular field should not be carried *too far* in the marginal fringes of medi[illegible]
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which constitutes a resynthesis of the important elements in the field of cardiology.

In using this encyclopedia, the physician must let go of his inclination to be taught, and cultivate the art of selecting new items of information and fitting them into a frame of reference dictated by his needs. This method does require a capacity for mental independence and is effective only in so far as this is exhibited by those for whom the encyclopedia is intended. Admittedly a work of this sort represents a form of communication in which there is much redundancy. At what point will the evil of redundancy equal or exceed the good contained in the message? Herein lies a very real problem with which we should be concerned in the future.

It is noteworthy that in the compilation of this work we are more dependent upon an editor than upon an author. The choice of Dr. Luisada to edit the work has been fortunate. He has exhibited not only a natural talent for this task but also the quality of persevering in the face of difficulties. To him alone belongs the credit for bringing the encyclopedia to fruition. The present handbook must be regarded as a monument to his genius.

ASHTON GRAYBIEL

Preface

This work was started as a result of a bold and far-sighted initiative of Dr. Ashton Graybiel, then president of the American College of Cardiology.

The task of editing an encyclopedia of cardiology represents a challenge which is both appealing and frightening.

Among the multitude of books of cardiology which have been published in the last 20 years, the majority belongs to the type of the medium-sized, monographic textbook written by a single author. A few have been written in collaboration by several authors. These, however, do not attempt to be complete and are, moreover, too unsystematic to be helpful Being of the "fixed-volume" type, they are soon outdated and, therefore, forgotten.

In ancient Greece, *encyclopaedia* meant "instruction in the whole circle, or complete system of learning" In a more restricted sense, encyclopedia means "a system or classification of various branches of knowledge, a subject on which many books have been published." While many encyclopedias of the past have been of the "alphabetical type" (each word to be explained is listed in alphabetical order), others have tried to reconcile system with completeness. Thus, even in the early editions of the *Encyclopaedia Britannica,* the various sciences and arts (such as anatomy or surgery) were "digested into distinct treatises or systems." On the other hand, technical terms were explained in alphabetical order Older encyclopedias, like Plinius's *Natural History* of the year 77 A.D. (37 books with 2,493 chapters) or *Yung-Lo Ta Tien,* the Chinese *encyclopedia of* 1403 A.D (11,095 volumes prepared in four years by over 2,000 scholars), were developed according to system. The latter even included well-known books reproduced without change.

In the opinion of the editor, a modern encyclopedia of cardiology *ought to* have the following characteristics: (1) It should encompass all available knowledge on the heart and vessels, including *history, embryology,* anatomy, *physiology,* physical and technical methods of examination, bacteriology *and pathology,* clinical sciences, surgery, pharmacology and therapy, rehabilitation, and the various "*allied fields*" (2) It should present them in a systematic order, thus permitting easy consultation (3) It should be *of the loose-leaf* type, in order to keep abreast of medical progress. It is then possible that some of the readers may prefer to call this a *treatise*

The principle of extending the work to all kinds of knowledge in the cardiovascular field should not be carried too far *in the marginal* fringes of medical or technical sciences This process would divert and distract the attention of the reader and would render consultation too difficult Therefore, a process of selection and limitation is an important part in the preparation of an encyclopedia of

cardiology. It is likely that a four-volume, 5,000-page encyclopedia would represent the optimal size. However, practical considerations indicate a more limited approach for the first version. Therefore, a four-volume, 3,600-page size is considered for the first edition, even though gradual revision and extension over the following ten years will probably increase the size to that previously mentioned.

Several titles have been considered for this encyclopedia. The one preferred by the editor, *Encyclopedia of Cardiology*, has been discarded for fear of discouraging prospective readers. The more modest title which has been selected—*Cardiology*—emphasizes the main scope [knowledge about the heart (and vessels)] even though it has a more modest sound than the original title. The titles of the four volumes have been selected on the basis of their content.

The problem of correlation has been the rock on which many textbooks written by multiple authors have foundered. If the various parts do not follow a logical sequence; if some of them are disproportionately long or short; if some are written by obscure authors of poor talent while others are the result of the work of well-known authorities; then the whole encyclopedia has no value.

In order to obviate these possibilities, the following steps are necessary: (1) the authors selected should be among the best, (2) each should receive a carefully selected and clearly outlined job, and (3) the editors should be able to refuse, abbreviate, or send back for correction any received text. Therefore, courage, patience, and hard labor are necessary to ensure a successful literary production.

The outcome of the work depends to a large extent upon the selection of authors. Well-known authors who have left a mark in the history of cardiology are the natural choice. However, they may be reluctant to undertake a major task and, moreover, may not be able to ensure continuity on account of their age. A compromise may be represented by asking these authors to prepare the text in collaboration with one of their associates. The associate would be the natural choice for any future revision of the text. However, a different author may entirely revise a chapter at a future date.

Science is international. If a truly objective work is to be published, authors of all nationalities should be asked to contribute. The recent tremendous progress of cardiology in the North American continent may require that a majority of the authors be selected in the United States and Canada. However, numerous contributors have been selected from England, continental Europe, Mexico, South America, Africa, and Asia, so that a truly "global" representation of cardiology may result.

How much of the text should reflect generally accepted viewpoints, how much should present new ideas still awaiting confirmation? This problem cannot be solved in a general way. The viewpoint of the editor is that an intermediate position should be preferred. Texts reflecting only generally accepted views might render the entire work obsolete within a few years. On the other hand, many new viewpoints cannot withstand the test of time and are gradually discarded. Whatever the error, whether in the sense of conservatism or in that of progressivism, a loose-leaf type of work may remedy it more rapidly than any standard type of volume.

The Editorial Board has been selected with great care according to these viewpoints:

1. Inclusion of a few authorities which would help in laying down the directives of the work.

2 Selection of persons with diversified knowledge (physiology, pathology, pediatrics, surgery, etc.), so that all fields may be covered by competent editors.

3. Choice of as many young scientists as possible, in order to have a high potential of enthusiasm, criticism, and working capacity.

The final product will reveal whether these directives are sound and have been followed as closely as possible.

The publication of this encyclopedia was made possible by the continued support of the American College of Cardiology through the action of its board of trustees, by generous contributions of five pharmaceutical houses, and by the warm collaboration of the McGraw-Hill Book Company, Inc., Blakiston Division.

Contents

VOLUME 1: NORMAL HEART AND VESSELS

PART 1: DEVELOPMENT AND STRUCTURE OF THE CARDIOVASCULAR SYSTEM

PART 2: CARDIOVASCULAR FUNCTIONS

PART 1

Development and structure of the cardiovascular system

1

Embryology of the heart and major vessels

JAMES G. WILSON

The organs of the vascular system are among the earliest to begin their development and appear to be the first to assume their functional role

During the first week of its existence, the human embryo relies for nourishment upon its meager inherent stores After implantation within the uterus early in the second week, nutritive materials and oxygen from maternal sources become available, but these must first traverse the surrounding trophoblastic wall and then, by diffusion, reach the individual cells. Rapid increase in size and complexity during the third and fourth weeks renders such processes as diffusion ineffective in distributing the materials necessary for continued growth and in eliminating accumulated wastes Thus arises the need for an intraembryonic system for transporting metabolites, and, coincident with this need, the *vascular system* is established in its basic form during the *fourth* week of embryonic life.

Angiogenesis. Since the development of the heart is intimately related to that of blood vessels, a brief consideration of angiogenesis, or blood vessel formation, is warranted It begins in the human embryo about the eighteenth day of gestation and is at first limited to such extraembryonic sites as the yolk sac, body stalk, and chorion The earliest recognizable vascular elements are *blood islands*, consisting of tight clusters or linear aggregates of cells (*angioblasts*) within the otherwise loosely organized extraembryonic mesoderm of these regions. The cells composing the blood islands soon become rearranged, so that the more peripheral ones are joined together to form a continuous flattened sheet of *endothelium* enclosing the more centrally placed ones which remain suspended in a fluid medium as primitive *hemocytoblasts*. By confluence of the endothelial vesicles and tubes thus formed, capillary plexuses appear and spread throughout much of the extraembryonic region

Earliest Cardiogenesis. Clusters of *angioblasts*, resembling the blood islands of extraembryonic sites, develop in the presumptive cardiac region as early as the time of formation of the first somite, in embryos of about 20 days' gestational age (Fig 1-1). These clusters lie in that part of the embryonic disk beyond the developing head fold in a region best designated as "precephalic" At first, this region, like the remainder of the embryonic disk, consists of the three primary germ layers, *ectoderm, mesoderm*, and primitive *endoderm*. The mesoderm in this location, as elsewhere, soon is subdivided into two layers by the appearance of a coelomic cleft, and since this is the cavity in association with which the heart will develop, it is called the *pericardial coelom*. Of the mesodermal layers, the one overlying the pericardial coelom and nearest the ectoderm, the *somatic mesoderm*, will contribute the pericardial wall; and the one more closely related to the underlying endoderm, the *splanchnic mesoderm*, will give rise to the heart wall Rapid proliferation in the splanchnic layer soon converts it to a thickened *cardiogenic plate*

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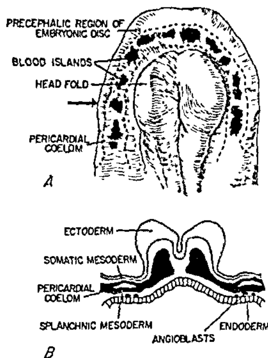


Fig. 1-1. Cephalic end of one-somite human embryo. A. Dorsal view of embryonic disc showing schematically the position of the pericardial coelom (outlined in broken lines) in relation to the head fold. Blood islands are represented (solid black) as if the overlying layer of ectoderm and mesoderm were transparent (Modified from Davis, 1927). B. Transverse section through A at place indicated by arrow.

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Between the cardiogenic plate and the underlying endoderm of the yolk sac, the first intraembryonic angioblasts appear and there proceed to elaborate the endothelial tubes about which the heart is formed As far as is known, the process of angiogenesis in this region is basically the same as that described for the extraembryonic areas. In any case, a plexus of endothelial tubes comes to occupy the space between the cardiogenic plate and the endoderm. From these first irregular tubes, two parallel channels emerge to run along either side of the head fold, one under each arm of the U-shaped cardiogenic plate. Accompanying formation of the endothelial tubes, the lateral arms of the plate move closer together and fuse at the midline, first in the precephalic region, then beneath the head fold, as the latter rises above the general level of the embryonic disk. The splanchnic layer of mesoderm is thereby converted into a single continuous sheet, the *myocpicardial mantle*, although the two arms of the original cardiogenic plate retain for some time their identity as prominent folds, one overlying each of the two main endothelial tubes. The symmetrical arrangement of these cardiac primordia along either side of the midline is the basis for designating this as the *double-tube stage*.

EXTERNAL DEVELOPMENT

Double-tube Stage. Although this stage (characteristic of embryos of about 21 days' gestational age with two to six pairs of somites and measuring 1 to 2 mm) has neither chambers nor surface markings suggestive of the familiar form of the future heart, certain of its features may be tentatively identified in terms of definitive structures (Fig. 1-2). Along the lateral and ventrolateral surface of the myoepicardium is a series of bulges arranged in a roughly symmetric fashion and separated from each other by sulci of varying depths. The most cephalic pair of bulges represents the region in which the *truncus arteriosus* will form, and, next in order and almost indistinguishable from the former, is the vaguely defined region of the *conus arteriosus*, a slight elevation near the center of the ventral surface of the myoepicardium The caudal part of the conal region blends smoothly with the two *ventricles* on the ventral surface, but laterally the juncture of these regions is clearly marked by the *conoventricular sulci* It should be noted that the left sulcus is deeper than the right, a condition foreshadowing the sharp flexion of the *cardiac tube* at this point in later development As the cardiogenic folds continue laterally from the ventricles into the *primitive right and left atria*, they are deeply creased by the *AV sulci*. The right sulcus is deeper than its counterpart on the left in this instance, a feature also of importance in connection with the future flexion of the cardiac tube. After a short course laterally, the myoepicardium covering the atria passes into the pericardium, but the endocardial tubes within the atria continue as venous buds beyond the pericardium, where they terminate blindly near the base of the yolk sac The precise future of these surface markings, however, is less certain than the derivatives of the layers in the heart wall, the present endocardial tubes give rise to the future endocardial lining,

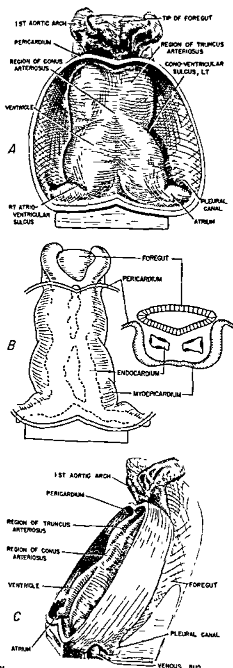


Fig. 1-2. The double-tube stage. A. Ventral view with the parietal pericardium mostly removed to show the myoepicardial mantle and its bilaterally arranged bulges and constrictions which roughly approximate future cardiac regions B The myoepicardium is represented as if transparent to show the relation of the two underlying endocardial tubes, and in transverse section to show relationships of myoepicardium and endocardium to the foregut C Lateral view to show the continuation of the endocardial tubes beyond the cephalic limits of the pericardium as the first pair of aortic arch arteries.

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Emerging from the cephalic end of the heart is the *first pair of aortic arch arteries,* which course along the ventral aspect of the foregut toward its tip, where each passes laterally to join the paired *dorsal aortas* on the dorsal surface of the foregut. Like the rudimentary veins at the atrial end of the heart, these arteries are direct continuations of the endocardial tubes (Fig. 1-2B). These, together with subsequently formed aortic arches, will form a succession of paired connections that pass through the branchial arches flanking the primitive pharynx to convey blood from the truncus arteriosus and ventral aortas to the dorsal aortas

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The heart does not long remain in the precephalic region where it first appeared. While the first few pairs of somites were forming and the heart itself was being organized into the double-tubed stage, the entire precephalic region of the embryonic disk, including the heart and pericardial coelom, swung ventrally through an arc of somewhat more than 90° to attain a subcephalic position This change was secondary to mechanical rearrangements associated with the rapid growth of the embryo As the embryonic disk enlarged in all direc-

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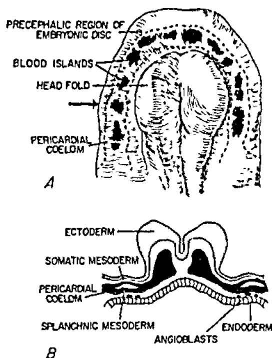


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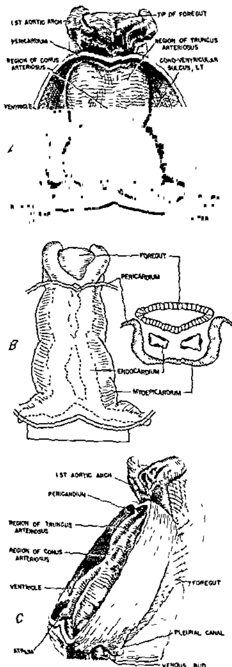


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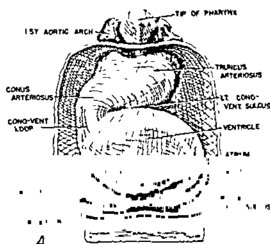
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tions, especially along its cephalocaudal axis, it soon overhung the yolk sac vesicle, which had enlarged relatively little. As the central portion of the disk continued to expand in a plane tangential to the yolk sac, the precephalic area of the disk was swung hinge-fashion from its position on the surface of the yolk sac to a new position underneath the rapidly elongating head fold.

Early Single-tube Stage. This stage is typical of embryos of about 23 days' gestational age with 8 to 11 pairs of somites and a greatest length of 2 to 3 mm The earlier bilateral character of the myoepicardium has been lost as the two cardiogenic folds have blended indistinguishably with each other across the midline in all regions except the extreme cephalic and caudal ends, i.e., in the regions of the truncus arteriosus and the atria (Fig. 1-3A). External appearance has been further altered by the development of two pronounced flexures along the longitudinal axis of the cardiac tube, since these flexures are in opposite directions, they create the effect of an S-shaped curvature The more cephalic of these is made up of the conus arteriosus and the major portion of the ventricle and is called the *conoventricular loop* It projects to the right and ventrally into the pericardial cavity, so that it has pulled away from the foregut to which the entire heart was closely attached earlier. Inspection of the loop from the lateral aspect (Fig. 1-3B) reveals that its pulling away from the pharynx has drawn out a double sheet of pericardium to form a suspensory ligament, the *mesocardium* This is, however, a transitory structure and begins to break down soon after it forms. A second flexure is seen where contiguous parts of the two atria and the primitive ventricle project toward the left as the *AV loop* (Fig 1-3A). This loop, unlike the preceding, remains closely applied to the ventral wall of the foregut In subsequent development, the atria will move in a cephalic direction relative to the remainder of the heart, so that they and their venous tributaries will finally come to lie dorsal to the ventricle.



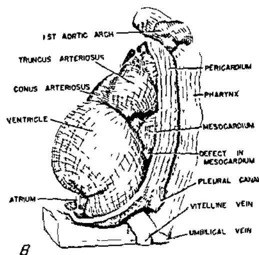


Fig. 1-3. *Early single-tube stage with most of parietal pericardium removed. Seen in A, ventral, and B, lateral, views.*

These early flexures of the cardiac tube are not random occurrences but constitute a regular and significant event in the over-all developmental pattern This is the first indication of asymmetry in the embryo It may well initiate hemodynamic or other physical factors that account for the later appearance of sidedness in the heart and the major vessels Its importance in determining asymmetry in other asymmetric viscera such as those of the respiratory and digestive systems is not clear *Situs inversus* is known to affect the heart alone in some instances and, in others, to be associated with abnormal sidedness in some or all of the remaining asymmetric viscera There seems little question, however, that the typical S-shaped curvature of the cardiac tube, with the conoventricular loop projecting ventrally and to the right, and the AV loop, dorsally and to the left, determines the normal left-sided position of the mature heart, and that a reversal of this curvature results in *situs inversus cordis* or *dextrocardia*.

Outside the pericardium, the endothelial buds that extended from the atria (Fig 1-3B) have been joined on either side by the umbilical

and vitelline veins, which have grown into the cardiac region from the body stalk and yolk sac respectively. The site where the two veins join the atrium on each side may be considered as a rudiment of the *sinus venosus*, or, more precisely, a horn of the sinus venosus Strictly speaking, the sinus venosus does not appear until later when, as a result of confluence of the present horns at the midline, a common vestibule forms on the dorsocaudal aspect of the atrial region to receive all the systemic veins approaching the heart

At the cephalic or arterial end of the heart, the first pair of *aortic arches* remain as the only branches leaving the truncus arteriosus until, in embryos of 10 or 11 pairs of somites, *endothelial* sprouts appear near the origin of the first arch arteries. These represent the beginning of the second aortic arches, but they do not become complete connections between the truncus and the dorsal aortas until somewhat later

Convoluted Single-tube Stage. This stage is found in embryos of about 26 days' gestational age, with 16 to 20 pairs of somites and a greatest length of 2 5 to 3 5 mm Although basically *still a* single tube, continued flexion and differential growth have brought the various regions of the cardiac tube to positions suggestive of their definitive relationships (Fig 1-4) The conoventricular loop has elongated to the extent that it now comprises the entire ventral surface of the heart, and the AV loop, particularly its atrial component, has expanded to make up a large portion of the dorsal aspect

The *mesocardium* that formerly suspended the heart from the ventral surface of the foregut has disappeared, and the tube is attached only at the arterial and venous ends, where the *myoepicardium* remains continuous with the *pericardium*. At the cephalic, or arterial, end, the *truncus* arteriosus projects a short distance beyond the limits of the pericardial cavity before terminating in the first pair of aortic arches Near the base of the first pair, the *second pair of aortic arches* has arisen and, like the former, passes around either side of the foregut to join the respective dorsal aortas The ventricular segment is beginning to show some degree of dilatation, foreshadowing its transformation to form the entire left ventricular chamber and a portion of the right ventricular chamber Beyond the ventricle, the cardiac tube turns dorsalward into the bilobed, *primitive atrium* The transition is marked by an AV *sulcus*, a landmark which will persist in the mature heart as the coronary sulcus

The atrial region is now best examined from the dorsal aspect (Fig 1-4B), where its original bilateral character is accentuated by lateral dilatations separated by a median groove, the *interatrial sulcus* Caudal to the pericardial reflection that encircles the base of the atrium,

vessels which approach the sinus from a caudolateral direction, where they receive the right and left umbilical and vitelline veins, respectively The sinus communicates with the atrium

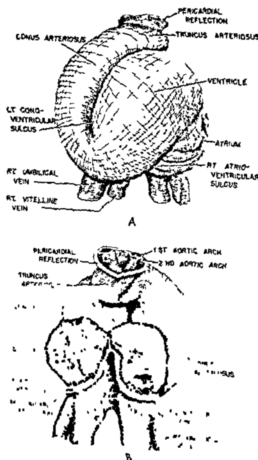


Fig 1-4. Convoluted single-tube stage removed from pericardial cavity in A, ventral, and B, dorsal, views At the arterial and the venous ends of the heart tube the pericardium has been cut along the line of reflection of the myoepicardium onto the parietal pericardium.

tions, especially along its cephalocaudal axis, it soon overhung the yolk sac vesicle, which had enlarged relatively little. As the central portion of the disk continued to expand in a plane tangential to the yolk sac, the precephalic area of the disk was swung hinge-fashion from its position on the surface of the yolk sac to a new position underneath the rapidly elongating head fold.

Early Single-tube Stage. This stage is typical of embryos of about 23 days' gestational age with 8 to 11 pairs of somites and a greatest length of 2 to 3 mm. The earlier bilateral character of the myoepicardium has been lost as the two cardiogenic folds have blended indistinguishably with each other across the midline in all regions except the extreme cephalic and caudal ends, i.e., in the regions of the truncus arteriosus and the atria (Fig. 1-3A). External appearance has been further altered

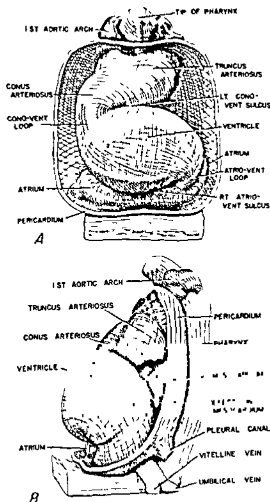


Fig. 1-3. *Early single-tube stage with most of parietal pericardium removed. Seen in A, ventral, and B, lateral, views.*

by the development of two pronounced flexures along the longitudinal axis of the cardiac tube; since these flexures are in opposite directions, they create the effect of an S-shaped curvature. The more cephalic of these is made up of the conus arteriosus and the major portion of the ventricle and is called the *conoventricular loop.* It projects to the right and ventrally into the pericardial cavity, so that it has pulled away from the foregut to which the entire heart was closely attached earlier. Inspection of the loop from the lateral aspect (Fig. 1-3B) reveals that its pulling away from the pharynx has drawn out a double sheet of pericardium to form a suspensory ligament, the *mesocardium.* This is, however, a transitory structure and begins to break down soon after it forms. A second flexure is seen where contiguous parts of the two atria and the primitive ventricle project toward the left as the *AV loop* (Fig. 1-3A). This loop, unlike the preceding, remains closely applied to the ventral wall of the foregut. In subsequent development, the atria will move in a cephalic direction relative to the remainder of the heart, so that they and their venous tributaries will finally come to lie dorsal to the ventricle.

These early flexures of the cardiac tube are not random occurrences but constitute a regular and significant event in the over-all developmental pattern. This is the first indication of asymmetry in the embryo. It may well initiate hemodynamic or other physical factors that account for the later appearance of sidedness in the heart and the major vessels. Its importance in determining asymmetry in other asymmetric viscera such as those of the respiratory and digestive systems is not clear. *Situs inversus* is known to affect the heart alone in some instances and, in others, to be associated with abnormal sidedness in some or all of the remaining asymmetric viscera. There seems little question, however, that the typical S-shaped curvature of the cardiac tube with the conoventricular loop projecting ventrally and to the right, and the AV loop, dorsally and to the left, determines the normal left-sided position of the mature heart, and that a reversal of this curvature results in *situs inversus cordis* or *dextrocardia*.

Outside the pericardium, the endothelial buds that extended from the atria (Fig. 1-3B) have been joined on either side by the umbilical

quired something of its future compactness (Fig 1-5C, D). The most significant aspect of this stage, however, is the formation of the *cardiac septa internally*; although external features may mark the position of the septa, they may not be reliable criteria of the progress toward ultimate partitioning. *Interventricular* and *AV sulci* mark only the approximate locations of the corresponding septal structures internally. The *aortopulmonary septal grooves*,

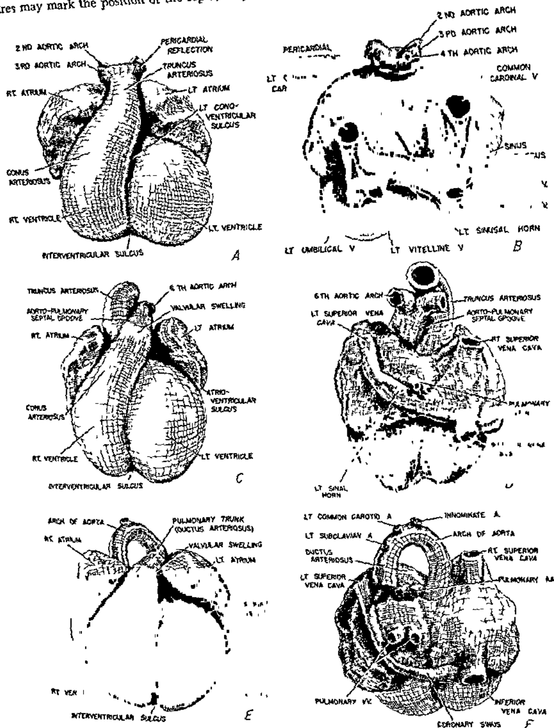


Fig 1-5. *Four-chambered heart Ventral, A, and dorsal, B, views at about 35 days Ventral, C, and dorsal, D, views at about 40 days. Ventral, E, and dorsal, F, at about 50 days.*

through the broad sinoatrial orifice, which is presently ill defined and centered at the midline; but, as development proceeds, this communication becomes more restricted in size and is shifted toward the right side, until it eventually empties only into the right atrial chamber.

Primitive Four-chambered Heart. This type of heart is found in embryos of about 35 days of age that measure 5 to 6 mm in crown-rump length The chambers are clearly indicated by localized dilatations in the cardiac tube, which has retained continuity between the segments but otherwise has lost its tubular character (Fig 1-5A, B). The *right* and *left ventricles* have developed from the conoventricular loop and the adjacent primitive ventricle, and further dilatation of the two halves of the primitive atrium has yielded the *right* and *left atria.* These expanded regions, although loosely referred to as such, are not yet "chambers" in the sense that they are partitioned compartments, as in the mature heart. Continued progression in a dorsocephalic direction has brought the atria to almost their final position relative to the remainder of the heart.

A prominent feature on the dorsal aspect is the *sinus venosus* with its complex of tributary veins (Fig 1-5B). The main body of the sinus has shifted toward the right atrium, into which it empties Its right horn is no longer recognizable as such, although the veins which it formerly received mark the region of the sinus into which it was absorbed The left horn persists and extends across the dorsal wall of the atria to the left side, where it receives the umbilical and vitelline veins of that side and, in addition, a new vessel, the *left common cardinal vein.* Comparable veins, including a *right common cardinal,* are also present on the right side, but the vitelline and umbilical veins on this side are larger than their counterparts on the left. At a slightly more caudal level, the umbilical and vitelline vessels on both sides are in process of being interrupted by the rapidly expanding liver. The resulting anastomoses in and around the liver tend to converge toward the right side, and particularly toward the right vitelline vein. Consequently, the terminal parts of both left-sided vessels, as well as the right umbilical vein, will shortly disappear as they become further deprived of the main flow of hepatic drainage, while the right vitelline vein remains to receive all the liver drainage and to form the terminal part of the *inferior vena cava.* Caudal to the liver, the two vitelline veins form about the gut a chain of anastomoses from which eventually emerges the solitary portal vein. After being interrupted by the liver, the right umbilical vein regresses but the left one continues to transport placental blood through the liver, first by random anastomoses with the vitelline veins and then by a direct channel, the *ductus venosus,* to the inferior vena cava via the hepatic veins. The common cardinal veins, which have appeared since the preceding stage, meet the need for venous return from the ever-increasing systemic circulation All the major veins associated with the sinus venosus come to terminate in the right atrium when the sinus is incorporated into the wall of this chamber. The *pulmonary veins,* the only ones normally draining into the left atrium, are not yet recognizable but may be foreshadowed by the appearance of an endothelial bud growing toward the lung buds from the dorsal wall of the heart

At the arterial end of the heart, a portion of the truncus arteriosus now projects cranially beyond the line of pericardial reflection surrounding it and terminates in a cluster of three pairs of arteries (Fig 1-5B) The most cephalic of these is the second pair of aortic arches, which has already passed its maximal development and persists only in fragmentary form The first pair, which was conspicuous in earlier stages, has regressed completely or been reduced to capillary caliber. Largest of the group is the *third pair of arches,* which serves temporarily as the principal channel between the truncus and the paired dorsal aortas. The most caudal of the arches is the *fourth pair,* which is now intermediate in size but will soon become largest of all the arches and is the pair destined to provide a permanent connection between ventral and dorsal aortas A sixth pair of arches may have begun to form, but at this time they would probably still be incomplete or plexiform. In man, the fifth pair is usually not seen and never appears as more than a vestige

Four-chambered Stage with Septa Forming. This stage is typical of embryos of about 40 days that measure 10 to 12 mm in crown-rump length. The chambers have filled out to such an extent that the course of the original heart tube is obscured, and the entire organ has ac-

quired something of its future compactness (Fig. 1-5C, D). The most significant aspect of this stage, however, is the formation of the *cardiac septa* internally; although external features may mark the position of the septa, they may not be reliable criteria of the progress toward ultimate partitioning. *Interventricular* and *AV sulci* mark only the approximate locations of the corresponding septal structures internally. The *aortopulmonary septal grooves*,

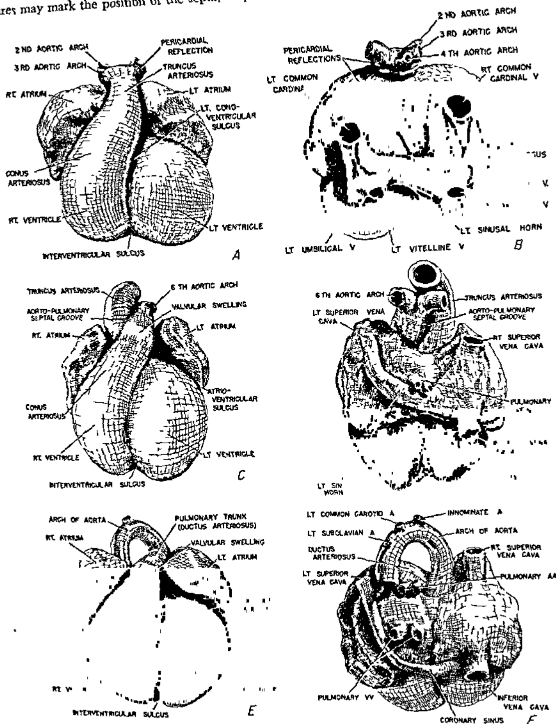


Fig. 1-5. Four-chambered heart Ventral, A, and dorsal, B, views at about 35 days. Ventral, C, and dorsal, D, views at about 40 days. Ventral, E, and dorsal, F, at about 50 days.

on the other hand, accurately mark the course and by their depth give some indication of the degree of completeness of the associated internal septum. When the truncus, conus, and ventricles are viewed from the ventral aspect, they collectively present a peculiarly twisted appearance (Fig. 1-5C). The effect is produced by the aortopulmonary grooves, which take a clockwise, spiraled course as they proceed caudally over opposite surfaces of these regions, that is, from the truncus over the conus and onto the ventricles. In the latter region, one of the grooves becomes continuous with the ventral, and the other with the dorsal end of the interventricular sulcus.

In the strict sense, the truncus remains undivided at this stage and continues for a short distance cranial to the pericardial reflection before giving rise to a pair of large arteries, the *sixth aortic arches.* Even before they were complete as arches, the ventral rudiment of each sixth artery gave a branch to the nearby lung bud, thus establishing these arches as the source of the *pulmonary arteries.* Further cranially, the truncus terminates in the large fourth and somewhat smaller third pair of arches The crotch between the truncus and the base of each sixth arch on either side is of particular interest because it is here that the aortopulmonary septal grooves and ridges begin and proceed caudally. At approximately the level where the conus and truncus are continuous, an externally visible swelling marks the region in which the aortic and pulmonary semilunar valves will form (see below).

The sinus venosus is no longer sharply outlined on the dorsal wall of the right atrium, having already undergone absorption into the right atrium (Fig 1-5D). The large *right superior vena cava* enters the heart at the cranial end of the sinal region. This vessel is a direct derivative of the former right common cardinal vein which earlier shared the cardinal venous drainage equally with its fellow of the other side An anastomotic channel, later to become the left innominate vein, has developed between the two precardinal veins, with the result that a large share of the drainage is shunted to the right, thus accounting for the disparity of size between the two venae cavae. Entering the caudal end of the sinal region is the *inferior vena cava,* which, in its terminal portion, was derived from the former right vitelline vein but which distally was compounded of venous channels from a variety of sources. It now receives blood not only from the gut and the placenta but also from the entire caudal half of the embryo. Approaching the sinus from the left side is the persisting left sinal horn, which appears to be a direct continuation of its only remaining tributary, the *left superior vena cava.* The latter was derived from the left common cardinal vein, but, with the shift of the venous drainage toward the right side, this vessel has become much smaller and will eventually disappear throughout most of its extent. The left umbilical and vitelline and the right umbilical veins have lost all direct connection with the heart.

A single *pulmonary vein* now enters the dorsal surface of the left atrium (Fig. 1-5D) as a short trunk that receives right and left tributaries from the right and left lungs respectively. It is usually recognizable somewhat earlier in embryos 6 to 7 mm in length. The single trunk now seen entering the left atrium is soon drawn into the rapidly expanding atrial wall, leaving its two tributaries to enter the heart directly.

Four-chambered Heart Nearing Completion. This heart is found in embryos of about 50 days of age that measure 18 to 20 mm in crown-rump length In so far as differentiation and formation of new structures are concerned, the heart at this early age is indeed near completion, but considerable growth and several modifications in proportion and contour are yet required to achieve the conditions found in the newborn infant (Fig 1-5E, F). The truncus arteriosus and the paired aortic arches have lost most of their former symmetric arrangement. The spiraled partitioning of the truncoconal region has converted what was a single arterial trunk into the *aorta* and the *main pulmonary artery*

On the dorsal aspect of the heart (Fig. 1-5F), the veins are rapidly acquiring definitive form and relationships. Both *superior and inferior venae cavae* empty directly into the right atrium, and the body of the sinus venosus into which the major veins drained earlier has completely disappeared into the wall of the atrium. The left horn of the sinus, however, remains and empties into the right atrium near the termination of the inferior vena cava The terminal portion of this horn, the part now

running transversely in the coronary sulcus, will become the *coronary sinus.* The much-reduced left superior vena cava normally continues to regress until it disappears throughout most of its length, except for the segment which runs obliquely across the left atrium This remains as the small *oblique cardiac vein* that empties into the coronary sinus In the event of incomplete regression of the *left superior vena cava*, it may remain as a functional vessel draining through the coronary sinus into the right atrium, or as a nonpatent cord, the *ligament of Marshall*

Two pulmonary veins instead of the one formerly seen now join the left atrium, and as the process of incorporation into the left atrial wall continues, the present two veins will be absorbed up to and beyond their respective points of bifurcation, thus resulting in the usual condition of *four separate pulmonary veins* emptying into the left atrium

The *coronary arteries* first appeared at a slightly earlier stage, at about 42 to 45 days, as solid endothelial outgrowths from the base of the aorta and grew rapidly through the epicardium overlying the cardiac sulci. By the ninth week, all the major branches found in the mature heart have appeared The *cardiac veins*, which drain into the coronary sinus, arise as endothelial buds from the sinus shortly before the appearance of the coronary arteries Like the arteries, the veins grow rapidly along the sulci to attain virtually definitive distribution by the ninth week The anterior cardiac veins which drain directly into the right atrium develop somewhat later.

By regression of some parts and retention of others, the aortic arches have been transformed into the asymmetric pattern characteristic of later life (Fig. 1-6A and B) As already seen, the first and second pairs regress at an early age, remnants of them may persist to contribute to formation of the *internal maxillary arteries*, in case of the first pair, and the *stapedial arteries*, in case of the second pair To describe properly the rearrangements associated with the third and fourth pairs, it is first necessary to point out that the cephalic end of the truncus arteriosus undergoes a progressive splitting into two bilateral branches, sometimes called *the ventral aortas*, each of which retains one of each third and fourth pairs of arches The sixth arches, however, are not separated laterally in this manner but instead are segregated from the other pairs by the formation of the aortopulmonary septum, as mentioned earlier. The right branch of the bifid truncus becomes the *innominate*, the *right common carotid*, and the *right external carotid arteries*, and the left branch contributes the *left common carotid*, the *left external carotid*, and that segment of the future *aortic arch* between the innominate and the left common carotid arteries Both fourth arches persist, the right as the first one-third of the *right subclavian artery*, and the left as the future *aortic arch* between the left common carotid and the left subclavian arteries. The third arch on either side contributes the proximal part of the *internal carotid* and probably some of the terminal part of the *common carotid arteries*

Following completion of the aortopulmonary septum and the concurrent splitting of the truncoconal region into aorta and pulmonary artery, the latter retained the sixth aortic arches and connected them with the *right ventricle*, thus forming the pulmonary trunk. The right member of the sixth pair of arches, however, regresses beyond the point at which it gives rise to the right pulmonary artery, leaving only the left to convey blood from the right ventricle to the dorsal aorta. This left arch persists until shortly after birth as the *ductus arteriosus*, but then it, too, normally regresses distad to the origin of its pulmonary branch.

Abnormal differentiation of the embryonic aortic arch system results in a number of anomalies involving the definitive arch of aorta and its branches. Among the commoner varieties are *abnormal right (retroesophageal) subclavian artery, right-sided arch of aorta*, and *double arch of aorta* (Fig 1-6C, D, and E), but several other abnormal patterns are known It has been suggested that normal differentiation of the system is dependent on hemodynamic factors, in other words, that the parts ordinarily retained are those through which stronger currents of blood are directed as they leave the heart and the truncus arteriosus. Conversely, anomalous development could be attributed to the presence of abnormal streams and eddy currents within the system, possibly resulting from a malformed or a malpositioned heart Indirect evidence favoring the latter possibility is the fact that anomalies of the heart and arch of aorta are often asso-

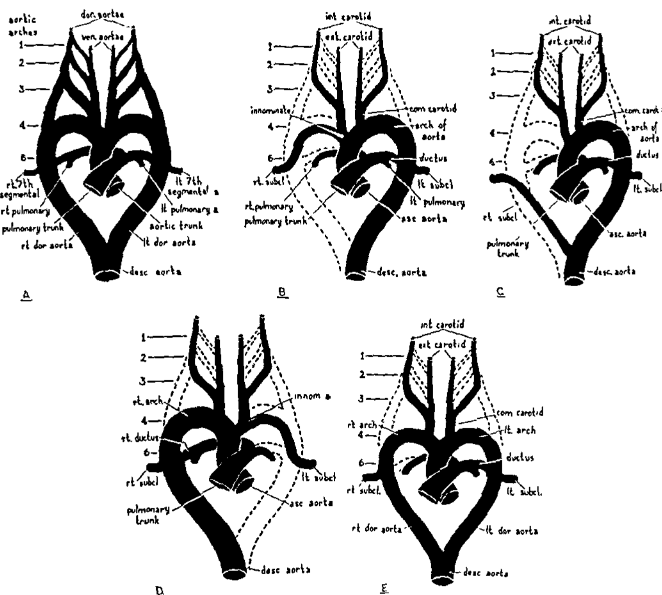


Fig. 1-6. Diagrammatic representation of differentiation in the aortic arch system. A Composite view of the arches as they would appear if all were present at one time B Definitive pattern of arteries resulting from persistence of some parts (black) and regression of other parts (broken lines) of the embryonic pattern. C. Abnormal right subclavian artery resulting from absence of the right fourth arch and persistence of the right dorsal aorta between the seventh segmental artery (to upper ext emity) and the descending aorta D Right-sided arch of aorta resulting from persistence of right instead of left dorsal aorta between the fourth arches and the descending aorta. E Double arch of aorta (vascular ring) resulting from persistence of both dorsal aortas between the fourth aortic arches and the descending aorta.

ciated in the same individual, but they are by no means invariably so related

INTERNAL DEVELOPMENT

Internally, the heart is lined by *endocardium*, the origin of which has already been described. During early stages (Figs 1-2, 1-3, and 1-4), the endocardium exists in tubular form loosely covered over by the myoepicardial mantle. While in the double- and single-tube stages, these two components of the wall of the heart are separated by a variable interval filled with an acellular matrix, the so-called *cardiac jelly*. For a time the cardiac jelly remains largely as a space filler between the myoepicardium and the endocardium, but, as the septa and other internal features begin to form, conspicuous numbers of cells appear in the cardiac jelly of such regions These concentrations of mesenchymal cells enlarge rapidly and soon cause the endocardium under which they lie to bulge into the lumen of the heart. Such internal

bulges, irrespective of where in the heart they appear, are known as *endocardial cushions.* Most of the internal structures of the heart are preformed in endocardial cushion tissue.

The chambers of the heart in embryos of 35 days are externally well defined, but internally they remain in free communication with one another (Fig 1-7A). The confluence of the two atria is only slightly restricted by the beginning *interatrial septum primum,* a ridge of endocardial cushion tissue growing inward from the dorsal and cephalic walls to delimit the *interatrial foramen primum.* In like manner the communication between the ventricles, the *interventricular foramen,* is beginning to be reduced by the *interventricular septum,* a slight ridge of cushion tissue growing inward from the caudal wall of the heart

A conspicuous feature on the dorsal wall of the right atrium is the slitlike opening of the sinus venosus which has now shifted from its earlier midline position Since the systemic veins of the entire body converge on the sinus venosus, the transfer of the latter brings all the systemic drainage into the right atrium. Bordering either side of the sinal orifice are two prominent folds, the *right* and *left sinal valves,* which unite at their cranial ends to continue along the cranial wall as a single fold, the *septum spurium* As the name indicates, the septum spurium is not truly a part of the interatrial septal complex, although its position and prominence at this stage would tend to suggest otherwise. The sinal valves and the septum spurium contribute little to future development, and for the most part they persist in recognizable form only in the *crista terminalis,* which, in the mature heart, marks the boundary between that part of the right atrium derived from primitive atrium and that derived from incorporation of the sinus venosus into the atrial wall.

A single small pulmonary vein may empty into the left atrium at this stage (Fig 1-7A) The origin of this vein until recently remained undetermined, but indications are that, as in lower animals, it arises as an endothelial bud that grows outward from the dorsal surface of the atrium Such an outgrowth would inevitably encounter the vascular plexus surrounding the foregut and the lung buds, which directly overlie the atrium Canalization of the endothelial outgrowth and the establishment of continuity between it and the plexus would permit drainage from the developing lungs directly into the left atrium. A normal pulmonary circulation in later life, however, would require that the original plexiform vascular pattern in the foregut region be altered so that venous drainage from the lung buds be separated from that of the remainder of the foregut, which empties into the systemic tributaries of the sinus venosus This separation is not always effected, with the occasional results that one or more lobes of lung retain venous drainage into the right atrium, either directly or through one of the major veins that were formerly tributaries of the sinus venosus Such pulmonary veins, whether they empty into a systemic vein or into the coronary sinus, are designated as *anomalous* or *abnormal pulmonary veins.*

The *atrioventricular (AV) canal* is a broad, transversely placed opening through which both atria communicate with both ventricles (Fig 1-7A). In keeping with the partitioning proc-

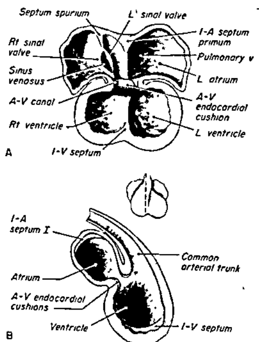


Fig. 1-7. A. Interior of the heart at 35 days, showing free communication between the four chambers and the beginning of certain of the septal structures, seen in frontal section B. The heart at 34 days, showing the beginning of several of the septal structures, in parasagittal section as viewed from the right side

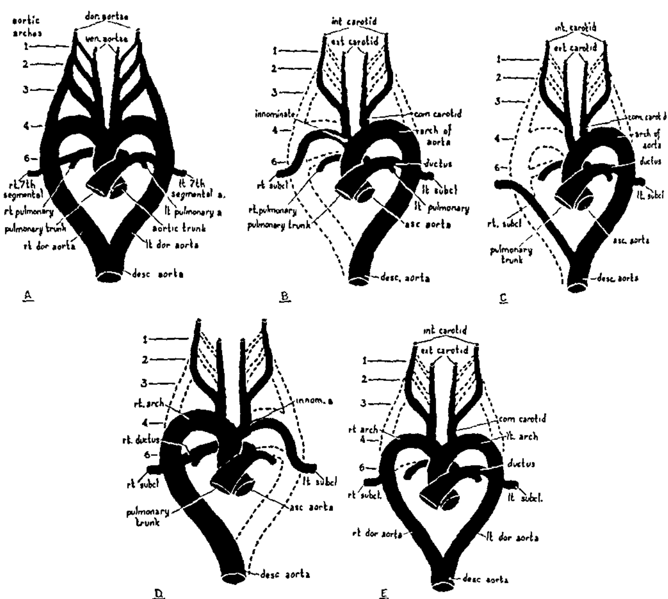


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component, may be regarded as substantially complete An interventricular foramen of modest size remains unobstructed, but the tissues which finally close this opening are derived principally from other sources, namely, the caudal ends of the two aortopulmonary septal ridges and the fused AV cushions, with little further contribution from the present interventricular septum The apposition and union of the AV cushions across the central portion of the AV canal has effected a division of this former broad passage into two narrower channels connecting the atria and ventricles of the respective sides. After completion of this process, a quantity of endocardial cushion tissue remains and is utilized, not only in helping to close the interventricular foramen, as already indicated, but also as a source of tissue for the formation of the AV valvular leaflets.

The *aortopulmonary septum* is likewise virtually completed, as the septal ridges have come together and fused throughout most of the truncoconal region Only in their most caudal portion, at a level corresponding to the origin of the aorta and pulmonary artery, do they remain unfused Nevertheless, interrupted development could still result in a minimal degree of the truncus communis defect, one located at or near the semilunar valves and usually designated as *aortopulmonary fistula* Other possibilities for abnormal development stemming from this stage are two different varieties of interatrial septal defect resulting from *persistence of either the foramen primum or the foramen secundum, or both Persistence of the interventricular foramen* in approximately its present condition accounts for the usual interventricular defect, in which only the membranous portion of the septum is deficient Valvula communis is no longer possible since the AV cushions have fused, but conceivably overgrowth or malalignment of the remnants of cushion tissue that contribute to formation of the right and left AV valves could result in *stenoses* or other malformations of these structures

By the end of the seventh week (about 48 days), the partitioning of the heart and its major arterial trunks is complete with the single exception of the interatrial septum (F- 1-8C) ...

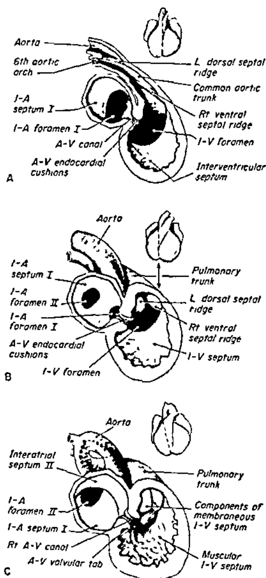


Fig 1-8 A The heart at 38 days, when the septal structures are developing rapidly but still permit free communication between the chambers, seen in parasagittal section B The heart at 42 days, showing the septal structures nearing completion, in parasagittal section Potentiality for maldevelopment will persist, however, until final closure of all presently existing communications between the right and left sides of the heart. C The heart at 48 days, seen in parasagittal section, after partitioning of the chambers is complete except for the interatrial communication, which is not closed until after birth. The interatrial septum secundum will continue to grow across the right face of the septum primum until the foramen secundum is obscured from view

esses beginning in the chambers, the canal also shows early indication of its ultimate subdivision. On its dorsal and ventral walls, *AV endocardial cushions* have appeared as a result of localized accumulations of endocardial cushion tissue. As the cushions enlarge, they reduce the central part of the slitlike AV canal, and when they ultimately meet and fuse, the original single channel will have been subdivided into *right* and *left AV canals.*

Further development of the septal structures that partition the heart into four chambers and, more significantly, into two separate circuits of blood flow, can best be visualized from the lateral aspect. Accordingly, a series of illustrations of embryonic hearts cut in parasagittal sections has been prepared to show the growth of the septa and their relationships to each other (Figs 1-7B and 1-8). The first of these illustrations (Fig. 1-7B) represents the septa in their earliest stages at about 34 days in development. It is clear that an interference with the further development of any of these would lead to severe functional impairment in later life. Failure of either the interatrial or the interventricular septa to develop beyond their present state would result in a three-chambered heart (*cor triloculare*), and failure of both would result in retention of the primitive two-chambered condition (*cor biloculare*) Lack of additional growth and ultimate union of the two AV endocardial cushions would leave the AV canal as a single transverse slit, *AV valvula communis*, a condition usually observed in the two-chambered, as well as the three-chambered, heart Since no septal structures are yet indicated in the truncoconal segment leading from the ventricles, cessation of development would leave this common arterial trunk (*truncus arteriosus communis*) to serve both the systemic and the pulmonary circuits

The septal primordia grow rapidly, and by the thirty-eighth day, the process of partitioning within the heart is moderately advanced (Fig. 1-8A), although large interatrial and interventricular foramens still permit free communication between the chambers of either side. Likewise, the AV canal still remains undivided, but endocardial cushions bulge prominently into the lumen and will shortly come into contact and fuse. In the truncoconal region, the *aortopulmonary septal ridges* have appeared as two spirally running folds of endocardial cushion tissue that project into the lumen from opposite sides of the arterial trunk A more complete account of these ridges will be given later; it is sufficient now to point out that they begin on either side where the sixth aortic arches arise from the truncus and follow a clockwise, spiraled course caudalward through as much as 225° to terminate in the region of the interventricular foramens Again at this stage, interference with development would cause severe abnormality. Large interatrial and interventricular foramens would persist if the related septal structures were arrested. Very likely, associated with either or both of these defects would be failure of the endocardial cushion to fuse. In fact, valvula communis persistens does not occur as an isolated abnormality but is always in association with some degree of interatrial and interventricular septal defect. Truncus arteriosus communis is still a definite possibility, since the aortopulmonary septal ridges have not united

By the end of the sixth week (42 days), all septal structures are well established and some are nearing completion (Fig 1-8B). The interatrial septum primum has grown caudally at the expense of the interatrial foramen primum, and the latter will shortly be obliterated when the septum reaches and fuses with the already fused AV cushions Before the foramen primum is obliterated, however, the dorsocephalic portion of the septum becomes thinned and then perforated to form the *foramen secundum.* The appearance of a second interatrial communication before closure of the first is essential for normal development of the heart Throughout embryonic and fetal life, the right atrium receives a great preponderance of the blood entering the heart, including not only the systemic drainage but the placental flow as well Conversely, the left atrium receives only the pulmonary venous drainage from the inactive and unexpanded lungs To compensate for this disparity of venous inflow, there must be a considerable transfer of blood from right to left atrium through an *interatrial foramen* at all times prior to birth In the absence of such, the left-sided chambers, both atrium and ventricle, become extremely hypoplastic and totally incapable of assuming their functional role upon the beginning of respiration after birth

At this time, about 42 days, the *interventricular septum*, or at least its future muscular

left fourth and left sixth arches remain to deliver blood from the heart to the descending aorta

The manner in which the right ventricle is brought into continuation with the sixth arch while the left ventricle is made continuous with the fourth arch is depicted in Fig 1-9 In foregoing discussions, the *aortopulmonary* septal ridges have been considered as though each were continuous from the region of the sixth arches to the conoventricular juncture. Actually, each ridge first appears in the form of three separate linear swellings, one in the proximal truncus, one in the region of the truncoconal juncture, and one in the conus, in embryos of 6 to 7 mm of length, and these are later united end-to-end as a continuous elevation The terminology sometimes applied is unnecessarily complicated, and for the present purpose, the two ridges are simply designated by terms that appropriately describe the relative positions of their cephalic and caudal ends. For example, the *right-ventral (RV) ridge* begins cephalically on the *right* side of the crotch between the truncus and the right *sixth aortic* arch, and courses caudally in a *clockwise spiral* through at least 225° to terminate on the *ventral wall of* the heart, where the conus joins the left ventricle. On the other hand, the *left-dorsal* (LD) *ridge* begins on the *left* side at the crotch between the truncus and the left sixth aortic arch, and follows an identically spiraled course to terminate on the *dorsal* wall of the conoventricular juncture. Both ridges, of course, ultimately *grow* caudalward to become *continuous with the* interventricular septum and, in so doing, aid in the closure of the interventricular foramen.

Returning to the exterior of the heart momentarily, the swollen region at approximately the truncoconal juncture (Fig 1-5C, D, E, F) was indicated in an earlier section as being the site of formation of the aortic and pulmonary semilunar valves, the *external valvular swelling*,

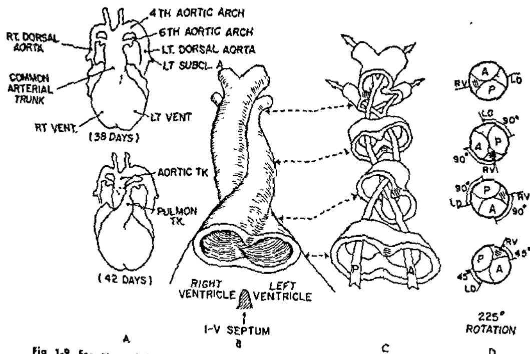


Fig 1-9. Formation *of the aortopulmonary* septal ridges A The heart and caudal part of the aortic arch system at 38 and 42 days to show the *development of the externally* visible septal grooves B. *Detail* of truncoconal region. C. Sections of the truncoconal region to show the changing position of the aortopulmonary septal ridges as *they spiral* in clockwise direction in proceeding from the sixth aortic arches toward the ventricular *region of the heart* D. Schematic representation of the *ridges* to show the degree of *spiral at different* levels. *LD*, Left-dorsal septal ridge; *RV*, right ventral ridge, *A*, aorta; *P*, pulmonary artery.

but it will be noted that the truncoconal grooves pass uninterruptedly across its surface Internally, the corresponding septal ridges also pass through this region, but the ridges are larger here than elsewhere because of greater accumulation of endocardial-cushion tissue. In addition, two endocardial cushions known as *intercalated valvular swellings* have appeared inside the walls of this region between the regular septal ridges. Thus, four endocardial cushions bulge into the lumen at this point in the truncoconal tube; but, here as elsewhere, only the bulges that are part of the aortopulmonary septal ridges grow across the lumen to unite with each other. After completion of the truncoconal septum, the resulting aortic and pulmonary compartments each contain one intercalated valvular swelling and one half of

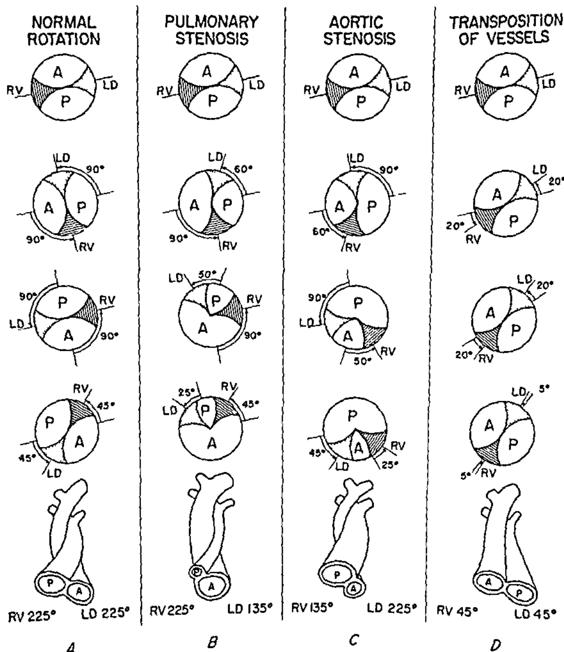


Fig. 1-10. Schematic representation of the normal partitioning of the common arterial trunk into aorta and pulmonary trunk of approximately equal size, A and B. A possible explanation of the origin of pulmonary *stenosis* is based on the assumption that one ridge, *LD*, rotates at a slower rate than its fellow, *RV*. C. A similar explanation for aortic stenosis is provided by assuming that the other ridge, *RV*, rotates at a slower than normal rate. D. If both ridges rotate at an equal but slower than normal rate, the result would be transposition of the great vessels

each of the swellings associated with the two septal ridges In other words, there are now three separate endocardial-cushion masses bulging into the lumen of the aortic, and three into the pulmonary trunks at the level of the external valvular swelling These will gradually be transformed into the three leaflets or cusps of the *semilunar valves* by the appearance of concave excavations on their surfaces farthest from the heart

The extent to which abnormal rotation of the aortopulmonary septal ridges may account for malformations involving the aortic and pulmonary trunks is an interesting subject for speculation In Figs 1-9 and 1-10, it is indicated that the normal relationships between [illegible] tery [illegible] both [illegible] in their spiraled, clockwise course from the sixth aortic arches to the interventricular septum If it is assumed that one of the ridges rotates at the customary rate while the other goes through somewhat fewer degrees of rotation in traversing its course, the outcome would be unequal division of the common arterial trunk (Fig 1-10B and C). It is proposed that *pulmonary stenosis* on the one hand and *aortic stenosis* on the other, depending on which of the ridges spirals downward at the slower rate, may result from some such aberrant processes. Rotation at equal rates but through fewer degrees than normally could account for *transposition of the vessels* (Fig 1-10D). A reversal of the direction of rotation also suggests interesting possibilities Although such mechanical schemes may appear to offer simple and adequate explanation of certain arterial anomalies, it must be emphasized that they are speculative and have not yet been substantiated by observation of abnormal hearts during development.

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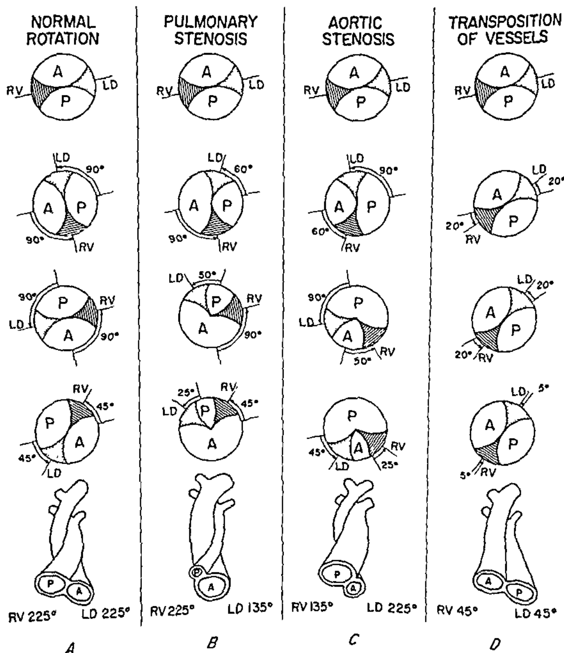


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A third anatomic characteristic of the fetal circulation needs to be mentioned, for it is the key to maintenance of an adequate placental circulation This is the presence in the umbilical recess of the liver (the termination of the umbilical circulation in the liver) of a recently discovered sphincter lying at the origin of the *ductus venosus* (Barclay et al). This structure commences to form in the 5-mm human embryo, and becomes fully formed and innervated by the twentieth week of gestation. This structure, which acts as a valve, serves, as we shall see, to keep an open circulation in the placenta

PHYSIOLOGICAL CHARACTERISTICS

Blood Pressure Gradients in the Fetus The gradient of systolic/diastolic pressures in the adult is well known There is a gradual fall in the large arteries, a large drop across the arterioles, and a relatively low pressure in the capillaries and the venous side of the circulation In the fetus, there is an important exception to this situation.

Direct observations in fetal lambs show the blood pressure to be about 70–75/50–55 mm Hg in the pulmonary trunk In the descending aorta, it falls to 65–70/45–50 mm Hg In the umbilical artery, there is further slight fall in pressure, to about 60/45 mm Hg From this point on, we find an important contrast to the usual situation across capillary beds, inasmuch as pressure in the umbilical vein is high for venous pressure, being about 20/18 mm Hg In the inferior vena cava, the pressure is at the normal level of 0–5 mm Hg A *region of resistance* to blood flow, therefore, exists between the umbilical recess and the inferior vena cava and it serves to keep pressure high *in the* umbilical recess The cause of this resistance to flow is twofold, one part being the sphincter of the ductus venosus, the other being the resistance to blood flow offered by the liver circulation, which is the alternate route of *blood flow* between the umbilical vein and the inferior vena cava if the sphincter is closed

Opening and closing of the sphincter has been seen to occur very rapidly when opaque material is injected into an umbilical vein and observed cineradiographically The degree of sphincter closure may be made to vary when venous return from the placenta is altered experimentally, although this is an observation which requires further study to shed light on its mechanism and significance.

The purpose served by maintaining a high umbilical vein pressure is that of keeping the umbilical vein well distended In this way, the umbilical vein possesses a large lumen which permits efficient flow of blood through the vessel. As a result of such distention, the entire placental circulation exhibits a *vis a tergo*, it is, in fact, an erectile organ (Reynolds, 1955).

Regional Blood Flow in the Fetus. Two recent estimates of the blood flow in different parts of the fetus point up its highly specialized character, adapting the fetus to life in utero. One study measured the proportion of the cardiac output going to the several regions of the body, the other, the velocity of blood flow throughout the organism.

Fifty-eight per cent of the total cardiac output leaves the left ventricle. *Of the total,* 15 per cent goes to the head and forequarters of the animal, 43 per cent goes down the descending aorta *Forty-two per cent of the* cardiac output leaves the right ventricle. Of this, 12 per cent enters the fetal lung, and the remaining 30 per cent joins, by way of the ductus arteriosus, the 43 per cent from the left heart to go down the descending aorta. Thus 73 per cent of the cardiac output passes to the caudal *end of the fetus Of this, 55 to 60 per cent goes to the placenta,* and 13 to 18 per cent goes to the hindquarters and abdominal viscera. On returning to the heart by way of the inferior vena cava, *46 per cent of the venous return goes through the foramen ovale,* and 27 per cent enters the right side of the heart. In *this* distribution of blood throughout the fetus is seen an adaptation to conditions which assure an ample blood flow through the placenta, with least flow to the fetal lungs The significance of this will be seen later

The velocity of blood flow in different parts of the fetus follows, in general, the volume flow *described* above Flow is most rapid in the umbilical vessels, slowest in the pulmonary arteries, slow through the head (though highly oxygenated, as noted above). If the blood flows most *slowly and* in least volume through the areas of highest vascular resistance, then it must be concluded that the peripheral vascular

The fetal circulation: changes at birth

SAMUEL R. M. REYNOLDS

Until the moment of birth, the fetal circulation possesses characteristics uniquely adapted to the "aquatic" environment of the fetus within the uterus. At birth, however, a series of changes takes place abruptly to permit the organism to breathe air. These changes necessitate a rerouting of the path of the blood circulation Such changes depend upon appropriate morphologic alterations taking place within the heart and great vessels If these alterations fail to occur properly, persistence of a fetal characteristic gives rise to one or another type of congenital malformation. In order to appreciate fully the necessary changes that normally take place at the time of birth, one must understand the characteristics of the fetal circulation

PATHWAYS OF THE FETAL CIRCULATION

The basic anatomic differences between life in utero and outside the uterus have been known since the days of William Harvey, early in the seventeenth century, although anatomists of an earlier time, extending back to the days of Galen in the second century A D., knew of one or another of the essential differences between the two conditions (Barclay et al.)

The heart receives blood through the large veins that enter it, and distributes blood to the arterial system In both the fetus and the newborn, blood enters the heart by way of the right atrium After birth, blood normally passes, as is generally known, to the right ventricle, and thence to the lungs for exchange of gases Oxygenated blood then returns to the left side of the heart for distribution in the systemic portion of the circulation

In the fetus, the blood that flows in the veins coming from the caudal part of the body is composed largely of oxygenated blood returning from the placenta Reaching the right atrium of the heart, the stream is divided into two by a protruding fold of tissue, the *crista dividens* One stream enters the right atrium, as in the adult, but the other passes through the *foramen ovale*, or *ostium secundum*, in the atrial septum In the left side of the heart, this blood, rich in oxygen, then is distributed into the systemic circulation by way of the ascending aorta Some of this oxygen-rich blood enters the vessels leading off the aortic arch to pass to the cephalic end of the body; the rest pours through the descending aorta to join the stream of blood from the right ventricle.

The right ventricular output, leaving by way of the pulmonary trunk, may go by either of two pathways Connection with the lungs by way of the pulmonary artery exists and connection with the descending aorta takes place by way of the *ductus arteriosus*, this structure links the pulmonary trunk with the aorta. We shall see below that little blood circulates through the fetal lung This fact is the key, in reality, to the maintenance of the fetal circulation and to the change-over which occurs at birth

A third anatomic characteristic of the fetal circulation needs to be mentioned, for it is the key to maintenance of an adequate placental circulation. This is the presence in the *umbilical recess of the liver* (the termination of the umbilical circulation in the liver) of a recently discovered sphincter lying at the origin of the *ductus venosus* (Barclay et al.). This structure commences to form in the 5-mm human embryo, and becomes fully formed and innervated by the twentieth week of gestation. This structure, which acts as a valve, serves, as we shall see, to keep an open circulation in the placenta.

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resistance of the fetal lung is very high. Conversely, in the placenta, resistance to flow is low (Reynolds et al, 1954).

Nervous Control of the Fetal Circulation. This has been a subject of study for many years (Barcroft, 1947). However, we may say that while much is known concerning the development of autonomic control of the fetal circulation, there remain to be discovered new facts which will reconcile important conflicting views.

The two views of the fetal autonomic system are essentially as follows: One view holds that for the last third of gestation (in sheep), there is a *progressive* increase and maturation in autonomic control of the circulation (Barcroft; Born et al.), rendering the heart rate and blood pressure progressively more efficient and exercising a more pronounced modulating action through the maintenance of sympathetic and vagal tone Admittedly, this varies with the several species, being developed in sheep but not in cats, rabbits, and dogs, which are less mature and have a lower blood pressure at birth.

The second view holds that although the cardiac accelerating and the vagal inhibiting mechanisms are complete at a rather early stage of development, they play no "tonic" role in the regulation of fetal heart rate (Reynolds et al., 1954) This view is based on these facts. (1) removal of the stellate ganglia or occlusion of the carotid arteries is without effect upon either fetal heart rate or the bradycardia induced by acute hypoxia; (2) induction of such distress gives rise to prolonged bradycardia which is abolished by atropine or section of the vagal nerves In other words, vagal tone may easily be induced in the fetus but is not present in the resting homeostatic state.

Fetal bradycardia in the lamb occurs (1) when the umbilical cord is occluded temporarily, (2) when the umbilical arteries are occluded, with a *rise* in fetal blood pressure; or (3) when the umbilical veins are occluded, with a *fall* in blood pressure. Barcroft, as well as Dawes et al. (1955), ascribes the slowing of the heart beat upon cord occlusion to an aortic-cardiac depressor reflex. However, the fact that the bradycardia occurs following venous occlusion which is associated with a fall in fetal blood pressure shows that such a reflex need not be involved. Bradycardia could result from acute hypoxia of the fetus due to interference with the placental blood flow. Supporting data have been obtained by Reynolds and Paul, who recorded the fetal blood pressure and heart rate of the fetal lamb in utero, with the membranes intact. In their experiments, hypoxia, which caused tachycardia and elevation of blood pressure in the ewe, gave rise to a vagal bradycardia in the fetus. Inhalation of oxygen, it was found, prevented bradycardia in the presence of otherwise adequate stimuli One must conclude, therefore, that the fetal heart rate is modified primarily by vagal influence which is sensitive to fetal hypoxia Slight hypoxia may induce an acceleration of fetal heart rate, as reported by Born et al, but this is a point which requires further study and confirmation.

After about 30 sec of severe hypoxia, the cardiac muscle is directly depressed, and it slows down This has been shown with a fully denervated fetal heart (Reynolds et al, 1954). After such a period of slowing, the fetal heart develops an extreme tachycardia under the influence of endogenous epinephrine, the tachycardia is prevented by adrenalectomy (Reynolds, 1954b).

Circulatory Homeostasis. It appears, therefore, that the resting heart rate of the fetal lamb is under very little nervous control, although the nervous connections exist and are capable of working. What is required to set them into action is a stressful stimulus This evokes a nervous effect which is short-lived, at best This view may require some modification in the light of further work and in view of the work of Dawes and his collaborators For the present, however, it is not clear how their observations under acute, highly experimental conditions apply to fetal homeostasis with the fetus in utero

THE NEONATAL CIRCULATION

Immediate Changes. Within the first 3 to 5 min, a series of changes takes place within the fetus which is basic and primary to all further changes in the fetal circulation

Cineradiographs of the fetal lamb show that with the first aeration of the lung, there is *a sudden increase in the rate of filling of the pulmonary arteries.* Whereas in the fetus, 10 to 15 cardiac ejections are required to fill these ves-

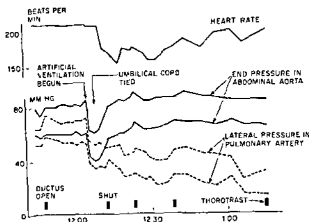


Fig 1-11. Record of blood pressure and heart rate in fetal lamb and at moment of aeration of lung Note that both pulmonary and systemic pressures fall immediately on aeration of the lung Cineradiographs showed ductus arteriosus open before ventilation and closed at all times afterward. End abdominal pressure was higher than lateral pulmonary pressure, an artifact of the recording technique Lateral aortic pressure in the fetus is lower (*From Ardran et al J. Physiol.* 1952)

sels with opaque material, immediately on pulmonary aeration, one cardiac ejection fills the pulmonary arterial tree The velocity of this filling is immediately four to five times faster than in the fetus Associated with this change, *pulmonary arterial blood pressure suddenly falls* (Fig 1-11) Thus, there is a profound increase of blood flow into the lungs under a low head of pressure. Since blood flows on the path of least resistance, we must assume that pulmonary vascular resistance is high in the fetus and far less high in the aerated lung Measurement of the factor of pulmonary peripheral vascular resistance by Dawes et al (1953) shows that it decreases by about 80 per cent within the first few minutes after aeration is begun

At the time that the above changes in the pulmonary arterial pressure occur, there is a rather extensive decrease in systemic blood pressure. This is transient, recovery taking place within 5 to 15 min The explanation for this decrease in systemic pressure at the time of increased pulmonary blood flow must lie in the fact that as the lungs expand they begin to hold more blood Consequently, diminished venous return to the left heart gives diminished cardiac output into the systemic circulation and an ensuing fall in systemic blood pressure occurs Measurements of the blood volume change in newborn fetal guinea pigs by Everett et al. show that there is an immediate increase of 20 to 30 per cent, followed by a further increase to 100 per cent in 24 to 36 hr. We find, accordingly, that the various facts regarding essential adaptive physiologic changes at the time of birth fit together These are summarized in Table 1-1.

MORPHOLOGIC ADAPTATIONS AT BIRTH

Ductus Arteriosus. Interest has long been attached to the time after birth when the

Table 1-1 Essential Adaptive Physiologic Changes at Birth

Factor	*Fetal condition*	*Neonatal condition*
[illegible]	++++	++
[illegible]	+	++++
[illegible]	++	+++ to +++++
[illegible]	++++	+

ductus arteriosus closes In general, there are three views: (1) weeks and months are required; (2) hours and days are required, (3) minutes only are required

It is well to state what is meant by closure. *Anatomic closure* to the passage of a probe requires many months. However, cineradiographs of the lamb and human being (Lind et al.) show that there is *functional closure* of the ductus arteriosus to the forward flow (pulmonary artery to aorta) of blood within the first minute or two after aeration of the lung is begun. Of this there is no doubt.

Recent work by Dawes et al (1955) shows that there is some return flow through a very restricted lumen in the reverse direction (aorta to pulmonary artery) *after* recovery of the systemic blood pressure. This reverse flow serves to shunt systemic blood into a relatively inefficient lung in the perinatal period There is no evidence that a similar reversal of flow takes place in the human being under normal circumstances. Attempts to record heart sounds and radiographs by Lind fail to show it. The fact that retrograde flow through a greatly constricted ductus arteriosus occurs normally in sheep suggests that it may occur in the human being on occasion. Significantly, if this were to occur and persist in the human being, clotting of blood, organization of connective tissue elements, and ultimate closure of the ductus would fail to occur. A condition of patent ductus arteriosus would exist.

Foramen Ovale. In order to understand the mechanism and the physical basis of closure of the foramen ovale (*ostium secundum*), one must know its essential anatomic character. It is an opening high up in the atrial wall, having a loose fold of mainly fibrous connective tissue overlying it in the left atrium The ostium secundum is in reality the end of the inferior vena cava, which is divided near its terminus by the septum of the atrial wall, this fold of tissue is the *crista dividens,* alluded to above. Normally in the fetus, as the greater, faster flow of blood from the inferior vena cava pours more than half its contents into the left atrium by way of the foramen ovale, the flaplike valve over the end of the inferior vena cava on the left side of the foramen offers no appreciable resistance to the flow of blood

Upon aeration of the lungs, the systemic blood pressure first falls, then, as noted above, it commences to rise while the pulmonary arterial pressure continues to fall. Measurements of the intra-vena caval and left atrial pressures throughout this time show that as the pulmonary circulation becomes reestablished after initial aeration, the left atrial pressure exceeds for the first time the pressure within the inferior vena cava. The flap valve is, therefore, forced shut against the foramen ovale and the blood in the inferior vena cava is forced into the right atrium.

It can be seen, therefore, that the timing of closure of the foramen ovale is secondary to the initial pulmonary circulatory changes It depends upon elevation of left atrial pressure to a level higher than that in the inferior vena cava.

Ductus Venosus. At present, there is no knowledge of when closure of this important circulatory pathway in the fetus occurs or of what forces bring it about.

PULMONARY VASCULAR CHANGES IN THE FETUS AT BIRTH

The key to the sequence of adaptive changes in the circulation at birth resides, as we have seen, in the nature of the pulmonary vasculature at birth and the changes it undergoes when the lungs become distended upon aeration. These changes have been elucidated by the author (Reynolds, 1956).

Fetal guinea pig lungs were fixed with the blood vessels full of trapped blood, as when functioning in situ Thick, 24-μ sections were then cut, and the hemoglobin was stained in order to reveal the arrangement of the blood vessels containing the erythrocytes. By this technique, the architecture of the fetal vasculature of the guinea pig lung has been revealed for the first time

Briefly, the arrangement may be described as follows: The branches of the bronchiolar arteries subdivide within the lobes of the lungs down to sudden terminal endings. Their inside diameters are about 20 to 30 μ At and near this termination arise numerous large capillary-like structures having five distinguishing characteristics. (1) They have large diameters, 20 to 30 μ across, and are packed with erythrocytes (Fig 1-12A) (2) They are tightly coiled and tortuous throughout their length, so that they are called *coiled arterial capillaries* They contain about them a network of juxtaposed

elastic connective tissue fibers. (3) They run in parallel relation to each other along the length of each alveolar duct, each coiled arterial capillary being in relation, therefore, to two or three alveolar ducts (Fig 1-12B). (4) They run directly into collecting venules. They make, therefore, direct, large connection between the arteries and the veins of the lungs, and they are virtually countless (5) Very important is the fact that they give rise along their lengths to an extensive capillary plexus that runs between two such coiled arterial capillaries In the fetus, these plexuses are collapsed and contain almost no erythrocytes

With ventilation of the lungs, two main changes take place The alveolar ducts become longer and larger Consequently, the coils of the arterial capillaries become uncoiled, and the distance between them, therefore, increases At the same time, the capillary plexus becomes extended in two directions, along and about each alveolar duct (Fig. 1-13).

What is the significance of the foregoing vascular arrangement and change to the early fetal adaptations at the time of birth? In the first place, the innumerable coils between arteries and veins open up, this will reduce the resistance to blood flow and will permit great acceleration in the rate and volume of blood flow into the lung (Table 1-1) Second, the opening up of a new and extensive capillary bed for the first time will take up an appreciable volume of blood This, then, will account for the initial increase in pulmonary blood volume, as shown in Table 1-1, and will cause a temporary decrease in the systemic blood pressure until the pulmonary situation becomes stabilized The fact that aeration of the newborn lung is partial and progressive as time goes on explains the gradual increase in pulmonary blood volume over the first 24 to 36 hr.

In this association of physiologic and morphologic facts, therefore, is seen the basis for the adaptations in the fetus at the time of birth, and also the explanation for the timing of these changes, viz., the closure of the ductus arteriosus and of the foramen ovale

MECHANISM OF CLOSURE OF THE DUCTUS ARTERIOSUS

The ductus arteriosus closes, as described, at the moment of fall of pulmonary and systemic blood pressure, secondary to the vascu-

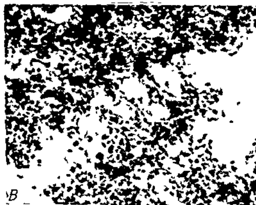


Fig. 1-12. A. Low-power section of a fetal guinea pig lung, cut at 24 μ Obtained as blood was trapped within blood vessels, and hemoglobin stained by a special dye, to show black in photograph Note long alveolar ducts around low portion of picture, and numerous coiled arterial capillaries running along the length of the ducts (From Reynolds Am J. Anat. 1956.) B The opened capillary plexus lying between convoluted arterial capillaries in a partially distended fetal guinea pig lung. This plexus lies about the alveolar duct

lar changes described above. There are three theories as to why the ductus closes One is that it is a reflex phenomenon; that some factor, or factors, associated with birth elicits a motor action of such a nature that the highly muscular walls of the ductus become contracted. These muscles are richly innervated. However, denervation and topical application of a local anesth...

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ments, but they are not essential for ductus closure.

The second hypothesis, described by Barcroft, is that the sudden increase in blood oxygen serves as a stimulus for ductus closure. If, as implied, this is a direct action of oxygen on the musculature of the ductus arteriosus, the

ductus arteriosus closes. In general, there are three views. (1) weeks and months are required; (2) hours and days are required; (3) minutes only are required.

It is well to state what is meant by closure. *Anatomic closure* to the passage of a probe requires many months. However, cineradiographs of the lamb and human being (Lind et al.) show that there is *functional closure* of the ductus arteriosus to the forward flow (pulmonary artery to aorta) of blood within the first minute or two after aeration of the lung is begun. Of this there is no doubt.

Recent work by Dawes et al. (1955) shows that there is some return flow through a very restricted lumen in the reverse direction (aorta to pulmonary artery) *after* recovery of the systemic blood pressure. This reverse flow serves to shunt systemic blood into a relatively inefficient lung in the perinatal period. There is no evidence that a similar reversal of flow takes place in the human being under normal circumstances. Attempts to record heart sounds and radiographs by Lind fail to show it The fact that retrograde flow through a greatly constricted ductus arteriosus occurs normally in sheep suggests that it may occur in the human being on occasion Significantly, if this were to occur and persist in the human being, clotting of blood, organization of connective tissue elements, and ultimate closure of the ductus would fail to occur. A condition of patent ductus arteriosus would exist.

Foramen Ovale. In order to understand the mechanism and the physical basis of closure of the foramen ovale (*ostium secundum*), one must know its essential anatomic character. It is an opening high up in the atrial wall, having a loose fold of mainly fibrous connective tissue overlying it in the left atrium The ostium secundum is in reality the end of the inferior vena cava, which is divided near its terminus by the septum of the atrial wall, this fold of tissue is the *crista dividens*, alluded to above Normally in the fetus, as the greater, faster flow of blood from the inferior vena cava pours more than half its contents into the left atrium by way of the foramen ovale, the flaplike valve over the end of the inferior vena cava on the left side of the foramen offers no appreciable resistance to the flow of blood.

Upon aeration of the lungs, the systemic blood pressure first falls, then, as noted above, it commences to rise while the pulmonary arterial pressure continues to fall. Measurements of the intra-vena caval and left atrial pressures throughout this time show that as the pulmonary circulation becomes reestablished after initial aeration, the left atrial pressure exceeds for the first time the pressure within the inferior vena cava. The flap valve is, therefore, forced shut against the foramen ovale and the blood in the inferior vena cava is forced into the right atrium.

It can be seen, therefore, that the timing of closure of the foramen ovale is secondary to the initial pulmonary circulatory changes It depends upon elevation of left atrial pressure to a level higher than that in the inferior vena cava.

Ductus Venosus. At present, there is no knowledge of when closure of this important circulatory pathway in the fetus occurs or of what forces bring it about.

PULMONARY VASCULAR CHANGES IN THE FETUS AT BIRTH

The key to the sequence of adaptive changes in the circulation at birth resides, as we have seen, in the nature of the pulmonary vasculature at birth and the changes it undergoes when the lungs become distended upon aeration. These changes have been elucidated by the author (Reynolds, 1956)

Fetal guinea pig lungs were fixed with the blood vessels full of trapped blood, as when functioning in situ. Thick, 24-μ sections were then cut, and the hemoglobin was stained in order to reveal the arrangement of the blood vessels containing the erythrocytes. By this technique, the architecture of the fetal vasculature of the guinea pig lung has been revealed for the first time

Briefly, the arrangement may be described as follows. The branches of the bronchiolar arteries subdivide within the lobes of the lungs down to sudden terminal endings Their inside diameters are about 20 to 30 μ At and near this termination arise numerous large capillary-like structures having five distinguishing characteristics. (1) They have large diameters, 20 to 30 μ across, and are packed with erythrocytes (Fig 1-12A) (2) They are tightly coiled and tortuous throughout their length, so that they are called *coiled arterial capillaries* They contain about them a network of juxtaposed

elastic connective tissue fibers (3) They run in parallel relation to each other along the length of each alveolar duct, each coiled arterial capillary being in relation, therefore, to two or three alveolar ducts (Fig 1-12B). (4) They run directly into collecting venules. They make, therefore, direct, large connection between the arteries and the veins of the lungs, and they are virtually countless (5) Very important is the fact that they give rise along their lengths to an extensive capillary plexus that runs between two such coiled arterial capillaries. In the fetus, these plexuses are collapsed and contain almost no erythrocytes.

With ventilation of the lungs, two main changes take place The alveolar ducts become longer and larger Consequently, the coils of the arterial capillaries become uncoiled, and the distance between them, therefore, increases At the same time, the capillary plexus becomes extended in two directions, along and about each alveolar duct (Fig 1-13).

What is the significance of the foregoing vascular arrangement and change to the early fetal adaptations at the time of birth? In the first place, the innumerable coils between arteries and veins open up, this will reduce the resistance to blood flow and will permit great acceleration in the rate and volume of blood flow into the lung (Table 1-1) Second, the opening up of a new and extensive capillary bed for the *first time* will take up an appreciable volume of blood. This, then, will account for the initial increase in pulmonary blood volume, as shown in Table 1-1, and will cause a temporary decrease in the systemic blood pressure until the pulmonary situation becomes stabilized The fact that aeration of the newborn lung is partial and progressive as time goes on explains the gradual increase in pulmonary blood volume over the first 24 to 36 hr.

In this association of physiologic and morphologic facts, therefore, is seen the basis for the adaptations in the fetus at the time of birth, and also the explanation for the timing of these changes, viz, the closure of the ductus arteriosus and of the foramen ovale

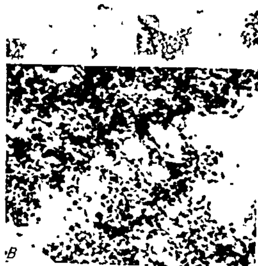


Fig. 1-12. A. Low-power section of a fetal guinea pig lung, cut at 24 μ Obtained as blood was trapped within blood vessels, and hemoglobin stained by a special dye, to show black in photograph Note long alveolar ducts around low portion of picture, and numerous coiled arterial capillaries running along the length of the ducts (*From Reynolds, Am. J. Anat* 1956) B The opened capillary plexus lying *between* convoluted arterial capillaries in a partially distended fetal guinea pig lung. This plexus lies about the alveolar duct.

MECHANISM OF CLOSURE OF THE DUCTUS ARTERIOSUS

The ductus arteriosus closes, as described, at the moment of fall of pulmonary and systemic blood pressure, secondary *to* the vascular changes described above. There are *three* theories as to *why* the ductus closes One is that it is a *reflex phenomenon*; that some factor, or factors, associated with birth elicits a motor *action of such* a nature that the highly muscular walls of the ductus become contracted. *These* muscles are richly innervated However, denervation and topical application of a local anesthetic agent do not prevent the ductus from closing when the lungs are ventilated. In short, the nerves exist, they are not histologic ornaments, but they are not essential for ductus closure.

The second hypothesis, described by Barcroft, is that the sudden *increase in blood oxygen* serves as a stimulus for ductus closure. If, as implied, this is a *direct* action of oxygen on the musculature of the ductus arteriosus, the

physiologist must invent a wholly new kind of muscle for which oxygen is an adequate stimulus for contraction. It is not such a stimulus for all other muscles of the body. If, as may be true, elevation of blood oxygen causes constriction of the ductus arteriosus, it could do so only by way of some nervous reflex action. If such be the case, the chemoreceptor organ for this action remains to be established.

The third hypothesis is a *mechanical* one. It is a fact that the ductus closes, in the absence of nervous action, when blood pressure falls throughout the body. If it is presumed that blood pressure in the ductus arteriosus in the fetus (which is high) holds open a ductus that is always trying to close, then when blood is diverted into the lungs on ventilation, and pulmonary and systemic blood pressure fall, the ductus will close. It is always trying to shorten and narrow, as is any muscular blood vessel. In extension of this idea, it is found that in an asphyxiated fetus the ductus arteriosus closes from an asphyxial spasm, overcoming an elevated pressure within the ductus arteriosus. In short, it appears that if the contractile force of the ductus exceeds the distending pressure of the blood within it, the vessel constricts Otherwise it remains dilated.

Upon constriction, the ductus shortens by about 20 per cent, its diameter decreases, and the walls thicken to the point where the internal elastic laminae become thicker and shorter, and the musculature, some of which is spirally arranged, shortens and becomes more circularly arranged. There is, therefore, a *structural reorientation* on constriction of the ductus arteriosus which, if it persists, enables a clot ultimately to form in the ductus arteriosus Later, this clot organizes into a fibrous scar and complete obliteration of the ductus is achieved.

Clinical Implications. The discovery that, at the time of birth, there is an extensive reorientation in the distribution of blood within the organism associated with opening up of a new vascular bed in the lung poses an inter-

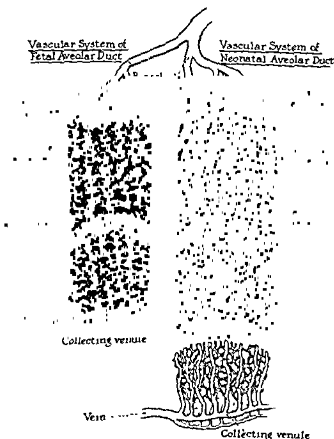


Fig. 1-13. Schema of the fetal (left) and neonatal vascular unit about the alveolar duct Note connection of large convoluted arterial capillaries between arteries and veins, and the net of capillary plexus between the convoluted arterial capillaries

esting clinical and physiologic problem, viz., is blood from the placenta beneficial to the fetus at the time of birth? If so, how?

It is not yet known how much blood is taken up by the aerated, neonatal lung. Experiments in sheep show that the more prompt and complete the recovery of systemic blood pressure after first ventilation, the more vigorous and prompt the recovery of the animal. Tying of the umbilical cord certainly aids this process by increasing resistance in two major arteries of the body. Likewise, lowering babies below the level of the placenta (still within the uterus) before clamping the cord enables them to gain 60 to 90 Gm in weight. This is in effect a transfusion of blood into the fetus. This can be as much as a 20 to 30 per cent increase in blood volume. Clearly, this transfusion will aid in the physiologic adaptations at birth, involving, as it does, hemodynamic changes throughout the fetal circulatory system. Other methods of getting blood into the baby have been suggested. How effective stripping the cord may be is not clear, but it may be helpful. Similarly, making the uterus contract by injection into the mother of an oxytocic prior to placental expulsion could conceivably be of value to the baby. The simplest demonstrated method, however, is to use gravity by holding the baby below the level of the placenta still in utero. There is some evidence that this procedure is of benefit during the perinatal period (Duckman et al.).

The original claim that placental blood is of benefit to the baby because it increases its iron reserves is, of course, valid. After birth, the baby obtains no iron until the diet is supplemented by meat. Increasing the amount of hemoglobin available at the time of birth alleviates any deficiency that might arise from such a cause. But to this nutritional benefit must now be added that of providing a volume of blood for an acute physiologic need which is inherent in the birth process. In nature, animals are born and drop below the level of the placenta, assuring that blood will pass into the fetus. So, too, among primitive cultures, women generally have their babies in an upright or a squatting position. Modern obstetric practice decrees, however, a position more agreeable to the physician. Physiologic adjustments within the fetus at the time of birth suggest that *there ought to be a reevaluation of current obstetric practices.*

Introduction to anatomic descriptions

NICHOLAS MICHELS

It is well recognized that constitutional anatomy is a constant variant, each body being different in regard to all the anatomic systems (cardiovascular, skeletal, muscular, nervous, lymphatic, urogenital, and digestive), and in regard to the structure of the organs of special sense (eye, ear, nose). Practically, all the newer surgical procedures have been based on a fuller and newer understanding of the pertinent underlying anatomy. This is especially instanced in bronchopulmonary resections, the intrapericardial approach to pulmonary vessels for removal of the lung, the intracardial approach to rectify congenital and acquired heart defects, and the resection and removal of abdominal organs

Among the successful surgical procedures are partial hepatectomies and hepatic lobectomies. As a surgical guidance, we now have a knowledge of the segmentation of the liver, comparable to that of the lung, and of the intrahepatic distribution of bile ducts and arteries. The latter was first demonstrated by Hjortsjo (1948), corroborated by Elias and Petty (1952), and statistically analyzed in corrosion casts of human livers by Healey and Schroy (1953).

More and more, roentgen anatomy brings to visualization, in the living body of young and old persons, *constitutional variations* and *functional distortions* caused by disease, neoplasms, congenital defects, developmental peculiarities, and factors of obstruction and infection. Through diagnostic radiology (cardiograms, x-ray films of the chest, cholangiograms, arteriograms, pyelograms, radiographs of various regions and organs), we now have a pretreatment and a preoperative picture of living topographic relations and of actually existent dynamic morphology and pathology of most regions of the body. Competence in reading and correctly interpreting expert roentgenologic records is based, mainly, on the ability to distinguish the normal from the morbid anatomy, and that item, in turn, necessitates an adequate, basic knowledge of constitutional variations.

Of all the *anatomic variations* met in the human body, none are more diversified, rampant, baffling, and, if surgically or clinically ignored, more impairing and destructive of life, than those of the arterial blood supply. This is particularly true if the variations are encountered in the thoracic or abdominal organs.

It is obvious that no one can remember all the arterial variations that have been encountered and recorded in the literature. Yet, in view of the progress made in modern medicine and surgery, it is also obvious that standardized descriptions and illustrations of regional and organal blood supply, as found in most texts of anatomy and surgery, are incomplete and inadequate. They should be improved by giving at least a workable familiarity with the most important and most common variants of arterial patterns. A laudable and deeply appreciated move in that direction is the exemplification of many variant arterial patterns in the newer atlases on anatomy (Grant, Anson), in Boyden's book, *Segmental Anatomy of the Lungs*, in Hollinshead's *Anatomy for Surgeons*.

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Arterial, like other anatomic, variations cannot be ignored, for they are ours to know, safeguard, and enjoy, not to belittle, neglect, mutilate, or destroy Halsted of Johns Hopkins University, a great pioneer who first introduced rubber gloves in surgery (1890), made this memorable and everlastingly true statement: "The surgeon's method of dealing with the blood vessels is a criterion of his proficiency in his art" (1921).

Arterial variations and their manipulations should be known, for the risk of ligating the wrong vessel or severing an essential organ-sustaining artery, along with the dangers of ischemia or bleeding are great, and, in many instances, have led to death of a patient, who otherwise would have survived had the operation not been performed (Lahey). As an axiom, it should always be remembered that the penalty of dalliance with existent variations in the cardiovascular system may be severe and even fatal.

Arterial variations are verifiable facts of human constitution that can be observed day after day, if only attention is paid to them and they are properly appreciated They have been estimated statistically by dissections of thousands of bodies and should, accordingly, be summarized in the lowest common denominators readily available to all fields of medicine, in particular to cardiologists and radiologists (for accurate diagnosis), and to surgeons (as a guide in operative procedures).

For this reason, in the subsequent presentation of the anatomy of the cardiovascular system, emphasis will be placed on the constitutional variants most commonly encountered in the arterial patterns. Topographic relations of the respective arteries will be described only when deemed necessary, viz, when they have not previously been sufficiently emphasized Only the most important and common vascular variants and the newer discoveries will be recorded, thereby serving the purpose for which this work was published.

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4

Anatomy of the heart

RICHARD H. LICATA

EXTERNAL CONFIGURATION

The heart is the main organ of the circulatory system, by it the circulation is maintained and from it blood is transported into the major arterial circuits for distribution to various parts of the body. Physiologically, the heart is a pulsating structure interposed between the two great arcs of the circulation, viz , the pulmonary and the systemic-visceral vasculature However, anatomically it is a *hollow, pyramid-shaped, muscular organ* lying within the middle mediastinum, enclosed in a serofibrous sac, the pericardium (Figs 1-14, 1-15). Because of its internal partitioning into *four* primary chambers. the external surface is divided into quadrants One pair marks the *venous end* of the heart, and is directed dorsally as a base in relation to the venous inlets The remaining pair of quadrants forms an apex lying relatively free within the pericardial cavity but is fixed at the arterial outlets Two dorsally disposed quadrants called the *atria* are separated internally by an *interatrial septum* and represent the venous cham-

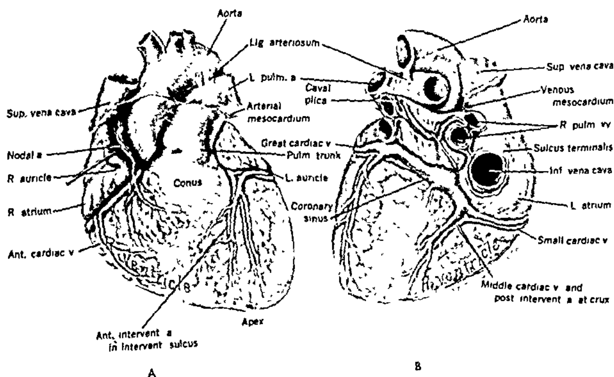


Fig. 1-14. A. Anterior view of heart. Right atrial appendage pulled to one side to show the sinoatrial artery. B. Posterior view of heart showing pericardial reflections.

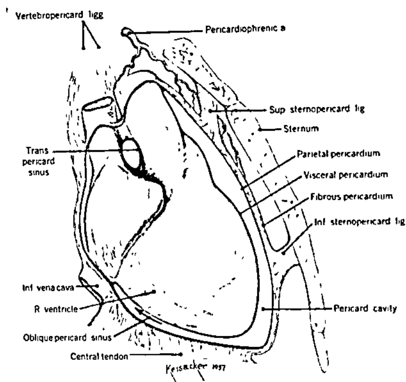


Fig. 1-15A. Right lateral view of heart in pericardial cavity

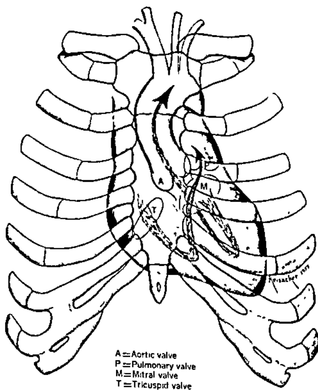


Fig. 1-15B. Topographic relation of heart and flow tracts

bers into which the major veins empty. The *ventricles* are similarly partitioned by an *interventricular septum* and constitute the greatest mass of the organ, representing the main pulsating portion responsible for propelling the blood into the great arterial trunks, viz., the *aorta* and the *pulmonary artery*.

Two venous trunks, called the *superior and inferior cavae*, enter the right atrium, into which they discharge the blood received from the systemic circulation Right and left pairs of *pulmonary veins* open into the *left atrium*, to which is returned the oxygen-replenished blood of the pulmonary circulation. The atrial, or venous, end of the heart is held suspended within the pericardial cavity by a supporting membrane, or venous mesocardium. The *mesocardium* is formed by duplicated folds of the pericardial lining which arise along the lines of position of the entering veins having their attachment along the mediastinal wall dorsally Thus a cul de sac or quadrilateral space referred to as *the oblique pericardial sinus* (Figs. 1-14, 1-15A) is constructed in direct relation to the left atrial wall. The central attachment of the mesocardium is comprised of a main vertical limb enwrapping the cavae and right pair of pulmonary veins (Fig. 1-15A). This attachment is almost directly in line with the interatrial septum internally and is significant in outlining a *central axis* for the heart.

As previously stated, two principal axes divide the heart topographically The quadrants thus established provide an architectural basis for orientation. The *central axis* runs through the heart from base to apex and lies essentially along the plane of orientation of the interatrial and interventricular septa The septa in question lie in a direct line in relation to each other and constitute a *septal complex* which forms a partition basally attached to the posterior mediastinal wall along the venous mesocardial membrane medial to the cavae. A plane is formed by the septa and caval mesocardium, which, if extended to the arterial end, would pass through the interval between pulmonary and aortic trunks. The chambers of the heart can be anatomically reconstructed around this assigned central axis, which deviates approximately 30° from the anteroposterior plane of the body as a result of a counterclockwise rotation involving the embryonic tubular heart prenatally.

A second partition containing valves can be observed running between the atrial and ventricular chambers, forming a *transverse atrioventricular (AV) axis* which crosses the former longitudinal axis midway between the two septa, thereby completing the segmentation of the heart The point of intersection of the transverse and central axes externally is called the *crux*, one lying anteriorly but hidden from view by the great vessels, and another, more significant, area lying posteriorly in relation to the dorsal cardiac surfaces at the level of the AV sulcus

Pericardial Sac. The middle mediastinum is outlined by a serofibrous membrane forming an enclosed cavity (Fig. 1-15A), in which is contained the heart. This limiting membrane is called the pericardial sac and is composed of two basic layers, viz , an external tough fibrous lamina (*pericardium fibrosum*) plus an internal smooth serous lining (*lamina parietalis pericardii serosi*). The outer supporting layer consists of a strong and resistant fibrous layer investing the roots of the great vessels as a tunic above, and is fused to the central tendinous aponeurosis of the diaphragm below The pericardium is thus in intimate contact with the great vessels, mainly at the level of the proximal parts of the superior vena cava, aorta, and pulmonary trunk, in these locations, the fibrous tissue of the pericardium gradually grades into the adventitia of these vessels. The heart, therefore, is an organ suspended within the pericardial cavity (*cavum pericardii*), preserving as its pedicle of fixation the great arteries and veins.

The serous layer (*pericardium serosum*) lines the entire pericardial cavity internally. The lamina parietalis is reflected over the roots of the great vessels in order to merge with an identical serous layer, the *epicardium* (lamina visceralis pericardii serosi), which covers the external surface of the heart Histologically, the fibrous pericardium is replete with intertwining, diagonally disposed, collagenous bundles organized at intervals into *fibrous bands* The thickness of the pericardial sac is thus not uniform, being composed of reinforced fibrous areas which alternate with comparatively weak membranous regions Numerous elastic fibers appear in the deeper layers

The fibrous pericardium is prolonged over the roots of the great vessels as a tubular in-

vestment but has its firmest singular attachment inferiorly at the central tendon of the diaphragm. Elsewhere, the pericardial sac appears relatively less fixed. The lateral surface of the pericardium adheres to the parietal pleura along its mediastinal border, thus forming a thin partition, the pleuropericardial membrane, separating pleural and pericardial cavities. This partition also transmits the phrenic nerve and the internal mammary artery with its associated pericardiophrenic and pericardial branches. The pleuropericardial membrane extends forward toward the ventral body wall as a continuous sheet which forms the lateral borders of the anterior mediastinum and encroaches on the pericardium across the midsternal line, except for an irregular, bare triangular area lying directly over the heart, particularly on the left. In this location, the pericardium is separated from the sternum over the cardiac notch area of the left lung by variable amounts of areolar tissue. The intervening connective tissue lying between the pericardium and its surrounding structures varies in thickness but may be sufficiently thickened in some areas to form ill-defined fibrous bands. However, the following supporting ligaments can be fairly distinctly identified connecting the sac with the surrounding structures.

Paired *sternopericardial* ligaments (*ligg. sternopericardiaca*) are present. A superior sternopericardial ligament passes from the fibrous pericardium at the level of the great vessels to the posterior aspect of the manubrium, whereas an inferior sternopericardial ligament passes from the anterior pericardial surface to practically the level of the xiphisternal junction. Right and left phrenicopericardial ligaments have been described arising from the diaphragm to attach to the lateral aspects of the pericardium basally, where they become incorporated in the fibrous tissue. These ligaments cannot be followed superiorly beyond the level of the hilum of the lung. A small fascia (*fascia of Morosow and Lowry*) situated anteriorly enables the pericardium to contact the peritoneum. Superiorly, paired vertebropericardial ligaments descend from the apical zone of the pericardial sac to merge dorsally with the prevertebral fascia adjacent to each side of the aortic arch.

Therefore, the pericardium is similar in construction to the serous membranes of the general body cavities. In particular, the pericardium resembles a closed sac into which the heart has invaginated to produce a lining. The reflection of parietal pericardium to epicardium occurs over the roots of the great vessels and is accomplished by duplicated sheaths, viz., the arterial and venous mesocardia (Fig. 1-11A), which arise dorsally as mesenteries in relation to the wall of the pericardial cavity. The dorsal mesocardial membrane is incomplete at one point, resulting in a transverse pericardial sinus (*sinus transversus pericardii*), an opening lying between the arterial and venous trunks connecting the right and left sides of the pericardial cavity.

In relation to the pericardial sac, the superior vena cava has a distinct extrapericardial segment, whereas in contrast, the inferior vena cava lies almost completely extrapericardially. The veins of the second pair of hepatic veins often are situated at the level of the diaphragm or just slightly above it. In the latter event, the pericardium contacts both the cava and the hepatic veins. The aorta and pulmonary artery slightly diverge from each other in the upper part of the pericardial cavity, and there is formed on each side a serous recess called on the right the *recessus aorticus* and, on the left, the *recessus pulmonalis*.

Within the lines of reflection of the venous mesocardium is a serous cul-de-sac, called the oblique pericardial sinus (*sinus obliquus pericardii*), which is directed posteriorly along the left atrial wall. The serous lining of the heart performs the function common to other similar structures by allowing limited unhampered movement of the enclosed organ within its sac. A small amount of lubricating fluid may be found within the pericardial cavity, which in reality represents a potential space. The fibrous pericardium is sufficiently lax so as not to encumber movement of the heart because of an inextensible pericardium.

The pericardial sac is related anteriorly to a paired potential space which has been mentioned in a previous paragraph. This space, known as the sternocostal triangle (or *space of Morosow and Lowry*), is formed by a gap in the diaphragm which contains the internal mammary artery in its descent to become continuous with the superior epigastric vessels. Two additional diaphragmatic hiatuses have a fairly close relation to the pericardial sac. One

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Pericardial Sac. The middle mediastinum is outlined by a serofibrous membrane forming an enclosed cavity (Fig. 1-15A), in which is contained the heart. This limiting membrane is called the pericardial sac and is composed of two basic layers, viz., an external tough fibrous lamina (*pericardium fibrosum*) plus an internal smooth serous lining (*lamina parietalis pericardii serosi*). The outer supporting layer consists of a strong and resistant fibrous layer investing the roots of the great vessels as a tunic above, and is fused to the central tendinous aponeurosis of the diaphragm below. The pericardium is thus in intimate contact with the great vessels, mainly at the level of the proximal parts of the superior vena cava, aorta, and pulmonary trunk, in these locations, the fibrous tissue of the pericardium gradually grades into the adventitia of these vessels. The heart, therefore, is an organ suspended within the pericardial cavity (*cavum pericardii*), preserving as its pedicle of fixation the great arteries and veins.

The serous layer (*pericardium serosum*) lines the entire pericardial cavity internally. The lamina parietalis is reflected over the roots of the great vessels in order to merge with an identical serous layer, the *epicardium* (lamina visceralis pericardii serosi), which covers the external surface of the heart. Histologically, the fibrous pericardium is replete with intertwining, diagonally disposed, collagenous bundles organized at intervals into *fibrous bands*. The thickness of the pericardial sac is thus not uniform, being composed of reinforced fibrous areas which alternate with comparatively weak membranous regions. Numerous elastic fibers appear in the deeper layers.

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Paired *sternopericardial ligaments* (ligg sternopericardiaca) are present A superior sternopericardial ligament passes from the fibrous pericardium at the level of the *great vessels* to the posterior aspect of the manubrium, whereas an inferior sternopericardial ligament passes from the anterior pericardial surface to practically the level of the sternoxiphoid junction Right and left *phrenicopericardial ligaments* have been described arising *from the* diaphragm to attach to the lateral aspects of the pericardium basally, *where they* become incorporated in the fibrous tunic These ligaments cannot be *followed* superiorly beyond the level of the hilum of the lung A small hiatus (*space of Morgagni and Larrey*) situated anteriorly *enables* the pericardium *to contact* the peritoneum Superiorly, paired *vertebropericardial ligaments* descend from the apical cone of the pericardial sac to merge dorsally with the *prevertebral* fascia adjacent to each side of the aortic arch.

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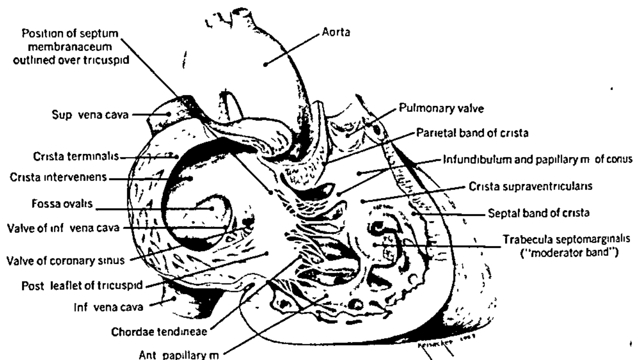
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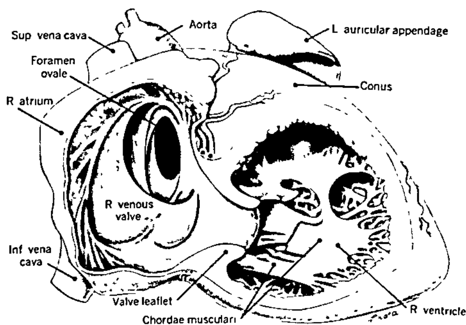


Fig. 1-16. A. Chambers of heart, opened on right side B. Figure of embryonic heart opened in the same manner.

lies dorsally in close proximity to the vertebral column and is referred to as the *vertebrocostal trigone*, or Bochdalek's gap. The second hiatus develops prenatally as an extension of peritoneum from the abdominal cavity into the thorax. Specifically, this sac of peritoneum, called the *infracardiac bursa*, protrudes into the right pleural cavity medially to the contained lung. Vestiges of the infracardiac bursa, trapped within the limits of the esophageal hiatus, can frequently be traced postnatally

Topography. The "lie" (Fig 1-15B) of the heart within the pericardial cavity presents three major surface areas that bear a topographic relation to the thoracic wall The *anterior* (facies sternocostalis) surface faces ven-

trally and corresponds principally to the right ventricular wall. The "*base*" of the heart (basis cordis) is directed dorsally against the mediastinal wall and represents the posterior surface comprised mainly by the left atrial wall. The *inferior*, or diaphragmatic, surface (facies diaphragmatica) is largely made up by that part of the left ventricular wall which is resting over the diaphragm. The right border of the cardiac silhouette in an anterior-posterior projection roughly describes a right angle having a perpendicular costal limb bending sharply to form an acute angle (margo dexter), as it leads leftward into a transverse limb or diaphragmatic margin The left heart border (margo sinister) curves more gently to extend well beyond the sternal midline, forming an obtuse angle whence it converges toward the horizontally directed *diaphragmatic margin* of the right border. The two lines of the heart contour meet at a point called the *cardiac apex*, which should be considered an anatomic part of the left ventricle lying at the level of the 5th interspace.

The spatial relationship of the *cardiac valves* with reference to their projection on the anterior thoracic wall can at best be regarded as approximate. This is particularly true when one considers the individual variations of heart contour encountered with respect to general body build. Anatomically, it is more pertinent to assign a base for the *ventricular* portion of the heart in preference to a base in terms of the organ as a whole A fibrous partition is formed for the base of the ventricles by *fibrous AV rings* bearing associated valvular leaflets which accommodate the venous ostia Normally, in the isolated heart, the annuli fibrosi are regarded as right and left structures, but in reality, in the intact heart lying in situ in relation to the thoracic wall, the afore-mentioned rings are situated approximately anterior and posterior with reference to each other The left ring, and its contained *mitral valve*, is dorsally situated, whereas the right ring supporting the *tricuspid valve* is directed ventrally. In a general sense, the valvular apparatus, with the exception of the tricuspid valve, rides over to the left of the midsternal line. The *pulmonary valve* is most superiorly situated, lying approximately in a horizontal plane at the level of the 2d interspace, or chondrosternal articulation, of the third rib In position, the *aortic valve* can be placed intermediate in position to the pulmonary and AV rings, being situated midsternally at the level of the 3d interspace on a plane oriented markedly oblique and inferior to the right margin of the former valve.

RIGHT CARDIAC FLOW TRACT. *Right Atrium.* The summated venous drainage of the systemic and visceral circulations is returned to the heart by way of the cavae to a common cardiac chamber, the right atrium After collecting in the atrium, the venous blood drains into the right ventricle, from which it exits by way of the conus arteriosus to enter the pulmonary circulation (*Figs. 1-16, 1-17B*).

At its point of confluence with the right atrium (atrium dextrum), the *superior caval* orifice is devoid of any valves and therefore opens freely into the atrial cavity. The inferior vena cava, upon leaving the abdomen and liver, has a short excursion within the pericardial cavity and enters the atrium from below. The mutual area of discharge within the atrial cavity, where the two cavae become confluent, is referred to as the *sinus venarum* (sinus venarum cavarum) and represents the original territory of the sinus venosus of the embryonic heart The two cavae are not directly in line in orientation, and the plane along the atrial wall dorsally, where the central axes of the two vessels apparently deviate from each other, is marked by a spurlike elevation of tissue which bulges into the atrial cavity. This elevation of tissue, called the *torus of Lower*, or crista intervenicns (tuberculum intervenosum), is not equally prominent in all hearts but, when present, extends as a ridge originating from the septal wall medially to the wall of the sinus venarum laterally The lateral boundary of the sinus venarum is formed by a prominent muscular ridge, the *crista terminalis*, which is delineated externally by a corresponding *sulcus terminalis*. Ribbonlike bands of cardiac muscle, called *musculi pectinati*, arise from the crista terminalis to fan out across the atrial wall. Unlike the ostium of the superior vena cava, the inferior caval orifice is guarded by a functionally incompetent valve, the *eustachian valve* (valvula venae cavae inferioris). For the most part, the valve of the inferior vena cava has its basal attachment along the crista terminalis The valve in question is in general widely perforated by irregular areas that give it a reticu-

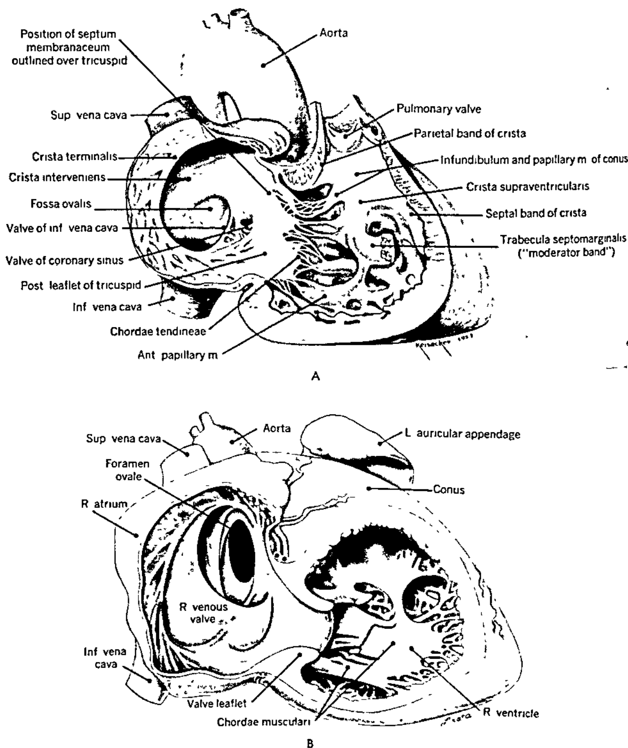


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lated appearance. The sinus venarum is completed by a cul de sac-like bay in the atrial floor which receives the orifice of the *coronary sinus* The margin of this atrial bay is usually provided with a diminutive flap of tissue guarding the orifice of the coronary sinus and called the *thebesian valve* This valvula of the coronary sinus (valvula sinus coronarii) is invariably irregular in form, like the valve of the inferior cava The territory of discharge around the mouth of the coronary sinus is partitioned from the inferior caval orifice by a bridge of tissue, the *sinus septum*. The sinus septum contains a fasciculus of atrial muscle referred to as the *inferior limbic band*. Associated with the inferior limbic band is a tendinous slip of tissue called the *tendon of Todaro* This ridge of tissue is continuous along the septal wall with the anterior eminence of a depression in the atrial septum called the *fossa ovalis*. Prenatally, the eustachian and thebesian valves are derived from one main valve of the sinus venosus which is strongly developed, particularly during the early stages of development. The right venous valve, as it is called in the embryonic condition, is normally reduced postnatally to give rise to the two afore-mentioned vestigial valves Incomplete resorption of this valvula during the regression process often gives rise to netlike remnants bordering the venous ostia, the orifices of the inferior cava, and the coronary sinus in particular. Such netlike formations, when excessively developed, are referred to as a *Chiari's net* and represent remnants of embryonic valvular structures

The crista interveniens has contained within it an atrial muscle fasciculus called the *superior limbic band*, which is directly continuous with the posterior eminence of the fossa ovalis. Subjacent to the crista interveniens, a pad of admixed fat and connective tissue may be found dorsally.

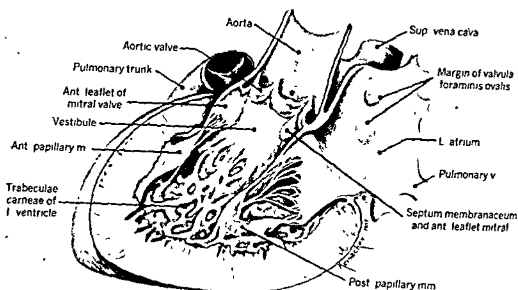
The medial boundary of the right atrium is represented by the *interatrial septum*. The dextral surface of the interatrial septum is relatively smooth except for a central depressed area as previously indicated, the *fossa ovalis*. The fossa ovalis marks the line of fusion of the original embryonic septum secundum with the valvula foraminis ovalis (septum primum) during the postnatal morphologic closure of the foramen ovale As already described, the fossa is circumscribed by a raised margin called the *limbus fossae ovalis (Vieussens)*. The limbus is customarily subdivided for descriptive purposes into anterior and posterior pillars. The orientation of the inferior vena cava is such that its orifice is distinctly inclined toward the face of the fossa ovalis. A saccular prominent extension of the atrium, called the *auricular appendage (auricula dextra)*, is prolonged anteriorly to complete the atrial chamber.

Right Ventricle. The general configuration of the ventricle may be roughly described as a triangular mitten-like outgrowth of the left ventricle. The right atrium meets the ventricle at the AV ring, a junctional zone guarded by a three-leaved valve, the *tricuspid*, which functionally serves to prevent regurgitation of blood into the atrial chamber. The valve is constructed of *anterior*, *medial*, and *posterior leaflets*.

The path of discharge of venous blood from the right atrium across the valvular apparatus into the homolateral ventricle represents the proximal inflow limb of the *right cardiac flow tract*. At the juncture of the anterior and medial leaflets, a valvular archway is formed which admits the entering stream into the body or sinus of the ventricular cavity. The ventricular body opens widely into a truncated sluicelike cardiac area called the *conus arteriosus* or *infundibulum* The arc of circulation of the right *cardiac flow tract* is completed distally by a terminal outflow limb having an excursion from the ventricular body into the conus arteriosus. The blood stream is apparently required to describe a gentle curve in order to negotiate the afore-mentioned valvular arch prior to entering the infundibulum.

The wall of the ventricle is considerably thicker than that of the atrium, and its internal surface is broken up by a profusion of myocardial bundles of irregular size. These muscle fasciculi, called *trabeculae carneae*, may protrude relatively free of the surrounding wall as a result of being undercut by extensive inter- [illegible]

[illegible] are made of cardiac muscle. However, some trabeculae are extremely attenuated and in contrast appear as pale fibrous strands, called "false" tendons or aberrant trabeculae. For the most part, these so-called false tendons contain a minimal core of myocardial tissue.



A

Caval mesocardium
Sup vena cava
R pulm v
Sinus venarum
Valvula foraminis ovalis
L atrium
Inf vena cava
R fibrous trigone
Septum membranaceum
Mitral valve
Septal leaflet of tricuspid
Bundle of His
Aorta
R at
L at
Septum musculare
Septum memb
Mitral
Tricuspid
Ant leaflet
Septal leaflet
Septum

B

Fig. 1-17. A. Chambers of heart, opened on left side B. Frontal view of heart showing all chambers.

LEFT CARDIAC FLOW TRACT. *Left Atrium* In relation to the right tract, the left flow tract of the heart lies essentially posteriorly. This is because the left atrial inflow chamber is directed dorsally and is almost totally hidden from view. The inflow arc of the left cardiac flow tract crosses the left atrium to enter the posterior half of the left ventricular cavity, whereas the outflow stream traverses the anterior segment of the ventricle to be ejected via the vestibule into the aorta, thus completing the right cardiac circuit of flow.

In contrast to the right atrium, the left atrium (Fig. 1-17A) is relatively smooth-walled internally, with the exception of *the auricular appendage* (auricula sinistra) and that portion of the atrial wall skirting the peripheral upper margin of the interatrial septum In these areas, bundles of muscle fasciculi similar to the *musculi pectinati* on the right, may be seen. The atrial chamber is oval in shape and *receives left and right pairs of pulmonary veins* which return the oxygenated blood from the pulmonary circulation to the heart The right pair of pulmonary veins bears a close relationship to the interatrial septum since it empties somewhat centrally in relation to the heart as a whole, and near the septal wall along its left side. The left pair opens laterally into the atrium.

The left face of the *interatrial septum* is more smoothly surfaced than the right. Over the area marking the position of the fossa ovalis on the opposite side, the fused attenuated remains of an irregular flaplike structure are frequently clearly delineated (Fig 1-17) This structural remnant, called the *valvula foraminis ovalis* (falx septi), is the vestige of the original valvula (septum primum) that adhered to the developing septal wall (*limbus foraminis ovalis* or septum secundum) during the morphologic closure of the foramen ovale which takes place postnatally The fused margins of this regressed valvula contain wide semilunar indentations of irregular size anchored by bands of tissue which fan out in sprawling fashion along the septal wall Occasionally, the scalloped margin of the valvula lies partly free of the septum, permitting passage of a probe across the fossa ovalis from the right into the left atrial cavity. "Probe patency" of the interatrial septum is commonly encountered and is due to incomplete fusion of the valvula foraminis ovalis with the septum Persistence of such an opening is a variation which is compatible with normal atrial pressures. However, increased pressure in the right atrium can be followed by right-to-left shunt in this condition.

Left Ventricle. At its entrance into the ventricle (Fig. 1-17), the left inflow tract is guarded by a dual-leaved valve named the *bicuspid* or *mitral valve*. Anterior and posterior cusps spring from the supportive fibrous ring at the junction and open into the ventricular cavity, where they insert by means of *chordae tendineae* into their corresponding *papillary muscles*. The anterior cusp of the mitral valve extends anteriorly and septalward into the ventricular cavity, whereas the posterior cusp is confined principally to the posterolateral periphery of the ventricular cavity. Structurally, the anterior leaflet and the noncoronary, *or posterior*, cusp of the aorta form a composite valvular complex that hangs curtainlike into the left ventricle The "lie" of the afore-mentioned valvular complex is such that it tends to partition the left ventricular cavity into halves. The posterior half of the cavity represents the path taken by the *inflow tract* in leaving the atrium, whereas the anterior half represents the *outflow tract* leading into the aorta. Thus from the posterior circumference of the aortic insertion, a fibrous membrane is suspended centrally into the ventricular cavity. The blood of the inflow tract must apparently negotiate a sharp bend around this membrane in order to exit by way of the outflow tract. In contrast to the normal picture of AV valves, the inferior or ventricular face of the anterior cusp is less populated with chordae tendineae, thus presenting less impediment to the blood stream entering the outflow tract.

The *posterior leaflet* is less strongly developed than its mate and is extremely variable. This leaflet is usually multiform, appearing to be comprised of a number of lesser valvulae presenting a festooned margin along the free valvular border.

Two major *papillary muscle groups* (Fig 1-17) project into the ventricular cavity. The anterior papillary muscle comprises a well-developed compact muscular mass whereas the posterior papillary group protrudes from the ventricular floor as a less regular mass. From the anterior papillary muscle mass spring the *chordae tendineae*, which diverge to insert along the intervalvular perimeter formed by the

A few trabeculae carneae are more strongly developed than the majority of the trabeculae and form muscular pillars from which spring *tendinous cords* that insert along the free margins of the AV valves, serving to anchor the valve leaflets in position. A constant *anterior* or *anterolateral papillary muscle* (musculus papillaris anterior) is formed from a unified group of trabeculae arising from the sternocostal wall of the ventricle. The remainder of the papillary muscles are relatively dwarflike in comparison and spring as diverse irregular groups from the ventricular wall. Septally, a diminutive papillary muscle of the conus (*Luschka*) may be found fairly constantly in a position commencing below the inferior margin of the crista supraventricularis. Both the anterolateral and conal papillary muscles serve to fix the anterior leaflet of the tricuspid in position. Several similar small papillary muscles (musculi papillares septales) arise serially below this level along the septum to the ventricular floor to serve for the attachment of the chordae tendineae of the medial leaflet. The *posterior papillary muscle* (musculus papillaris posterior) comprises a multiform group of relatively small members which take origin from the diaphragmatic wall of the ventricle.

A band of myocardium frequently leaves the septal wall close to the ventricular floor, from which it traverses the cavity to terminate by inserting into the ventricular wall laterally. Prior to reaching the ventricular wall, this bridge of tissue usually has a partial insertion in the base of the anterior papillary muscle. This modified trabecula is commonly referred to as the *moderator band*, although it has been variously designated as the *trabecula septomarginalis* (*Leonardii*) and the *limbic band of Gross*. The significance of this myocardial bridge is that, when present, it conveys the terminal part of the right stem of the bundle of His; it does not serve, as formerly fancied, to restrain the heart wall from overdistention.

The intertrabecular spaces form an intricate interconnecting labyrinth that reaches all points of the ventricular wall internally. These spaces have their deepest penetration along that zone where the ventricular wall and septum meet along the sternocostal line.

Infundibulum. The infundibulum, or *conus arteriosus*, constitutes the distal or terminal limb of the *outflow tract* that leads from the body of the ventricle into the pulmonary circulation. In contrast to the remainder of the ventricular cavity, its walls are relatively smooth, particularly in that part that comprises the floor of the tract. The floor of the infundibulum consists of a muscular shelf which is strikingly thinner than the remainder of the ventricular wall. This area, in reality, is a zone along which the posterior wall of the conus has fused with the adjacent anterior wall of the aorta to form a partition called the *aortic septum*. In general, wherever any two parts of the heart wall became juxtaposed, the tissues involved become rarefied. The pulmonary conus wraps around the insertion of the aortic root in this locality in gaining entrance to the pulmonary circulation. A robust, muscular ridge of the left ventricular wall underlies this area. This particular part of the infundibular wall can be readily freed from the adjacent portion of the left ventricle. The two muscular layers in question form an apical segment of the interventricular septum. Between the two muscular leaves of the aortic septum, blood vessels, nerves, and a variable amount of areolar tissue may be found.

Crista Supraventricularis. The *crista supraventricularis* (Fig. 1-16) is a well-developed muscular ridge representing the inferior margin of the conus arteriosus. The sluicelike conus, already described, lies above this level and is usually referred to as the infundibulum or the pulmonary outflow tract. Two well-defined muscular bands arise from this ridge, viz., a parietal or mural band and a septal band. The parietal band swings laterally and, proceeding inferiorly under the basal attachment of the anterior cusp, ends as a fasciculus partly surrounding the venous ostium. In cases of interventricular defects of the septum, the crista and the proximal part of the parietal band (which is frequently hypertrophied in these cases) form a prominent, funnel-shaped arch overriding the persistent opening. A second, more muscular, septal band arises from the crista to lose itself among the trabeculae of the muscular septum. The trabecula septomarginalis, when present, arises centrally from the crista or in close relation to the septal band. Of added clinical importance is the fact that a hypertrophy of the crista and its associated bands can result in stenosis of the infundibular ostium. A *pulmonary valve* marks the transition from infundibulum to pulmonary trunk.

LEFT CARDIAC FLOW TRACT. *Left Atrium* In relation to the right tract, the left flow tract of the heart lies essentially posteriorly. This is because the left atrial inflow chamber is directed dorsally and is almost totally hidden from view The inflow arc of the left cardiac flow tract crosses the left atrium to enter the posterior half of the left ventricular cavity, whereas the outflow stream traverses the anterior segment of the ventricle to be ejected via the vestibule into the aorta, thus completing the right cardiac circuit of flow

In contrast to the right atrium, the left atrium (Fig 1-17A) is relatively smooth-walled internally, with the exception of *the auricular appendage* (auricula sinistra) and that portion of the atrial wall skirting the peripheral upper margin of the interatrial septum In these areas, bundles of muscle fasciculi similar to the musculi pectinati on the right, may be seen The atrial chamber is oval in shape and receives *left and right pairs of pulmonary veins* which return the oxygenated blood from the pulmonary circulation to the heart The right pair of pulmonary veins bears a close relationship to the interatrial septum since it empties somewhat centrally in relation to the heart as a whole, and near the septal wall along *its left side* The left pair opens laterally into the atrium.

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three margins of the anterior and posterior leaflets. The posterior group of papillary muscles consists of two or three muscular heads of origin for the inelastic tendinous cords. In addition, a number of dwarflike papillary muscles are associated with the posterior leaflet. The chordae tendineae arising from these mural papillae set out to insert as before along the margins adjacent the valvular gaps.

The left ventricle is the most muscular member of the cardiac chambers. From the body of the ventricular cavity, the *outflow tract* leads into a *vestibule* or *subaortic sinus*, from which the blood enters the aortic outlet. Of all the cardiac chambers concerned, the left ventricle is the ultimate in design to perform with the maximum efficiency. Accordingly, its wall is the thickest muscular unit of the heart

Mention was made of the fact that the interventricular septum should be morphologically considered an integral part of the left ventricle. This anatomic arrangement can most readily be appreciated when a cross-sectional view of the two ventricles in normal relation is examined (Fig 1-22). The contour of the septum in such a view follows generally the concentricity of the left ventricular wall and, as a result, bulges somewhat into the right ventricular cavity, thus presenting a concavity to the left This is particularly true in hearts which were fixed in systolic contraction The right ventricle of such cases appears as an adjunct appendage comprising a lateral outgrowth from the left ventricle Indeed, the remainder of the cardiac chambers and their associated vessels can be systematically built around the left ventricle as a primary unit in reconstructing the heart as an organ

The vestibule, or subaortic sinus, is somewhat cylindric in shape and is fairly smooth-walled internally. It is the outlet cone of the left ventricle. In orientation, this outlet lies relatively ventral with respect to the remainder of the chambers The circumferential border of the zone in question consists of an anterolateral muscular rim completed by a posteromedial fibrous segment The muscular border is made up by the adjoining septum and lateral ventricular wall, whereas the fibrous border consists of the annular attachment of the anterior leaflet of the mitral valve and related septum membranaceum. The outlet is roofed over by the aortic valve situated at the entrance into the aortic trunk.

ARTERIAL OUTLETS. The outflow tract of the right ventricle is completed distally by a relatively short but stout *pulmonary trunk* (Fig. 1-18). A three-cusped *pulmonary valve* composed of semilunar valvulae ensures a unidirectional flow of blood into this vessel. The truncated appearance of the pulmonary artery accentuates the cone-shaped contour of the infundibular portion of the right ventricle from which it arises, adding still more to the contrast between the two ventricles. The pulmonary trunk ascends upon the left ventricle and bifurcates forthwith into *two main stems* at the level of the upper margin of the transverse pericardial sinus, directly superior to the roof of the left atrium. This primary relationship with the atrium is partly responsible for the relatively hidden position of this cardiac chamber in the anteroposterior view. The ejection of right ventricular blood thus describes an understandably brief course in reaching the pulmonary arteries because of this foreshortened span of the outflow tract Beyond the point of divergence of the main channel, the two lesser channels behave differently and should therefore be considered separately.

The *left stem of the pulmonary trunk* (Fig 1-18) describes an arch as it ascends briefly to form a promontory from which it extends dorsally and leftward to reach the hilus of its respective lung. The comparatively direct line of origin of this stem from the main vessel is aided by the fact that the *ligamentum arteriosum* arises from the medial margin of this artery proximal to its origin from the trunk and serves to give it a fixation that pulls it upward toward the arch of the aorta The primary branchings off the left artery, as a result of the ascent of the left vessel, appear to drop off acutely into the hilus of the lung, particularly in relation to the basal bronchopulmonary segments.

In contrast, *the right stem* (Fig 1-18) assumes a transverse orientation as it leaves the main trunk. The initial course of this stem is to curve sharply behind the aortic root in order to gain entrance into the posterior mediastinum, from which it passes closely behind the wall of the sinus venarum of the right atrium, approximately at the level of the crista interveniens

The right stem thus has an unrestrained excursion lateralward to the right where it divides into *primary ascending* and *descending branches*

The *aorta* comprises the main arterial trunk of the systemic circulation The configuration of this vessel (Fig 1-18) is most clearly appreciated from a full unhampered view of the implanted aortic trunk. The root of the aorta inserts into its own corresponding fibrous ring of the cardiac skeleton The aorta springs from that part of the left ventricle referred to as the vestibule. The insertion of the aorta is central in relation to the cardiac skeleton, and its fibrous base resembles a broad band of fibrous connective tissue rather than a distinct fibrous ring At its commencement, the root of the aorta presents three dilatations situated behind the semilunar cusps comprising the aortic valve. These *aortic sinuses* (*of Valsalva*) are areas of the aortic wall molded by the eddies which form during ejection and by the aortic pressure operating at this level in diastole. The uppermost limit of this circular band is scalloped in appearance where it meets the smooth muscle of the aorta and serves to give attachment to the basal margins of the aortic valve The *aortic annulus* can therefore be regarded structurally as a fibrous vinculum girdling the insertion of the aorta, from which also arise fibrous laminae that grade into the fibrous layers of the remainder of the cardiac skeleton The *coronary arteries* issue from the aortic wall at points slightly above the level indicated by the occlusal margins of the cusps of the respective valvulae Therefore, the forceful deflection of the aortic valvulae toward the vessel wall at the time of systolic ejection of blood can in no way be regarded as functionally impeding the entrance of blood into the orifices of the coronary vessels Upon expansion, the sinal wall of the *anterior* (*right coronary*) *cusp necessarily* protrudes into the infundibulum where it molds the parietal band of the crista supraventricu-

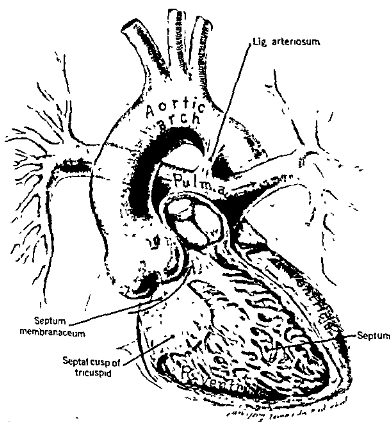


Fig 1-18 Arterial outlets of heart Right ventricular wall removed.

laris. The juxtaposed wall of the infundibulum is strikingly thinned out as it wraps around this part of the aorta. The dilatation adjacent the sinus, which corresponds to the *right posterior* (or *noncoronary*) *cusp*, abuts against a similar markedly thin portion of the medial wall of the right atrium, thus forming an aortic promontory in the atrial cavity. The commissural interspace between the afore-mentioned dilatations is occupied by an apical segment of a fibrous plaque called the *septum membranaceum*. Internally, this fibrous area is intersected on the right side by the basal attachment of the medial cusp of the tricuspid valve.

The general configuration of the aorta is that of a gentle arch arising from the left ventricle to descend into the thorax as an approximately midline vessel lying somewhat to the left of the vertebral column. An *aortic valve* composed of three semilunar cusps, similar to that in the pulmonary trunk, guards the entrance into the aorta The ascending aorta springs from the aortic root and in this segment runs upward with an inclination somewhat forward and to the right. A vaguely defined bulging along the right margin, when apparent, is referred to as the *great sinus of the aorta* and apparently marks the path of the most forceful projection of the entering blood stream during systole Beyond this point, the aorta bends gradually, forming an *aortic arch* that curves dorsally and from which originate the main arterial vessels to the upper part of the body Somewhat distad to the left subclavian artery, the aortic arch may normally appear perceptibly constricted This narrow segment is referred to as the *isthmic region* (isthmus aortae) and is the site of attachment of the ligamentum arteriosum, which inserts along the inferior margin of the aortic arch This narrowing reflects the fact that prenatally the diameter of the isthmic aorta is greatly reduced, because it is a bypassed segment of the aorta with a less active circulation due to shunting of most of the blood by way of the ductus arteriosus into the thoracic aorta beyond this point. Clinically, this area has added significance in that it is the favored site for occurrence of congenital coarctation in malformed hearts The proximal portion of the thoracic aorta widens somewhat as it descends in the mediastinum and receives the designation of *spindle aorta*.

VENOUS INLET. The atrial chambers of the heart receive the aggregated venous return from the systemic or pulmonary circulations Figure 1-19 presents a composite picture of the venous ostiums in their entirety. Prenatally, the two atrial chambers are in free communication by way of a common orifice, the *foramen ovale*, which at that time represents a special type of venous ostium. Postnatally, after obliteration of the foramen ovale, the two atrial chambers become separated by a muscular partition, the interatrial septum.

Into the right atrial chamber postnatally enter the summated systemic streams of the venous flow. The superior caval orifice opens freely and directly into the atrium The flow through the cava is augmented by an admixture from the azygos system (Fig 1-19). In addition, the illustration emphasizes the manner in which the ostium of the inferior vena cava is distinctly directed toward the fossa ovalis. The *pars membranacea* (valvula foraminis ovalis) of the interatrial septum is frequently not completely adherent to the septal wall, resulting in the type of "probe" patency previously described (Fig. 1-19) It is obvious that a strongly developed valve of the inferior cava, when present, would tend to act as a baffle, serving to deflect the blood stream toward the left through any persistent wide septal defect that might develop in this area

The relation of the visceral or hepatoportal circulation to the right atrium is also included in Fig. 1-19 The *portal vein* drains into the sinusoidal vascular field of the liver, indicated in transparency The venous return from the hepatic sinusoidal bed forms a confluens represented by the hepatic veins which consist of two or three venous roots which open into the inferior vena cava, usually somewhat below the level of the diaphragm. The added drainage from the *coronary sinus* completes the collection of venous currents in the right atrial chamber. The total circulation of the right atrium subsequently exits via the AV orifice to enter the right ventricle

Normally, two pairs of *pulmonary veins* converge on the left atrium (Figs 1-14B, 1-19), bearing oxygenated blood from the pulmonary circulation Each pair consists of a superior and an inferior pulmonary vein The left pair of pulmonary veins enters the atrial chamber lat-

erally. A small fold of tissue (Figs. 1-14B, 1-23B) skirts the atrial wall lateral to the left pair of *pulmonary veins* in order to ascend along the dorsal margin of the transverse pericardial sinus up to the level of the left pulmonary artery. This ligamentous fold is called the *left caval fold* (plica venae cavae sinistrae). It is comprised of a duplication of the serous layer of the pericardium and contains an attenuated vein referred to as the *oblique vein of Marshall* (vena obliqua atrii sinistri). The vein is frequently connected by means of a small tributary with the left superior intercostal vein. The oblique vein terminates by draining into the distal end of the coronary sinus. This venous arc is the shrunken remains of the embryonic *left superior vena cava*. Within the plica are also contained some areolar tissue and a rich plexus of nerves. In cases of persistence of a left superior cava, the interrelationship of this structure with the left pair of pulmonary veins is more strongly borne out.

Detailed delineation of branches of the pulmonary veins in the lung fields is complicated by their intricate relation to the arteries. Generally, within the lung, the smaller branches of

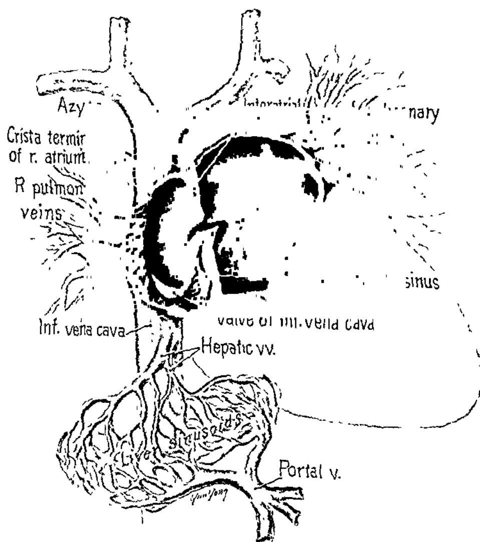


Fig 1-19. Venous inlets of heart shown in relation to cut atria

the pulmonary veins have a course similar to that of the pulmonary arteries which they accompany. These veins exit at the hilus where they unite to form the paired venous trunks (Figs. 1-14B, 1-19) previously described. In contrast to the arteries, the pulmonary veins pursue a relatively brief course before reaching the heart wall where they terminate by opening into the left atrium. On the right, the *superior pulmonary vein* passes posterior to the superior vena cava, whereas the *inferior branch* has a course behind the atrium at the level of the crista interveniens. In Fig. 1-19 the hilar and peripheral fields are shown only in part.

The right pair of pulmonary veins opens fairly centrally (Figs. 1-14B, 1-17B, 1-19) into the atrial end of the heart immediately adjacent to the left face of the interatrial septum. Because of its close relationship to the septum, it can readily be seen how this pair of veins is sometimes displaced rightward to open into the right atrium as a result of an interference involving the normal prenatal growth of the septum. When the latter condition is present, the hemodynamics operating in the area causes a left-to-right shunt (*anomalous pulmonary venous return*). Occasionally, three pulmonary veins are found on the right side, when the middle lobe vein drains independently into the atrium instead of uniting with the upper member of the normal pair. The oxygenated blood is discharged from the left atrium into the left ventricle through the left AV ostium The *bronchial veins*, which are extremely variable in position, usually open into the pulmonary veins, less frequently into the azygos veins. The musculature of the left atrial wall forms sparse spirals around the entrances of the pulmonary veins There is some suggestion that these coils of muscle may act as sphincters at the pulmonary orifices in order to prevent any significant reflux of blood back into the veins

SEPTAL COMPLEX. Anatomically, the combined septa of the heart constitute a central muscular axis (Fig. 1-17B) for the organ. The interatrial septum lies in a plane directly in line with that of the interventricular septum. However, the combined septa form a partition, the orientation of which is roughly dorsoventral in relation to the main body axis. From this standpoint, the cardiac walls can be regarded as being organized around this main structural axis Because of its approximately midline position, the caval mesocardium forms the main suspensory ligament for the interatrial septum and represents one of the principal mediastinal points of fixation for the septa as a whole. At the arterial end, the great vessels with their investing pericardial reflections constitute a second point of fixation By removing the paramedian walls of the heart from its central muscular partition, the full architecture of the septa as a complete unit can be clearly observed (Fig. 1-20A). In particular, cutting away the lateral walls features the precise orientation and configuration of the individual septa in relation to each other.

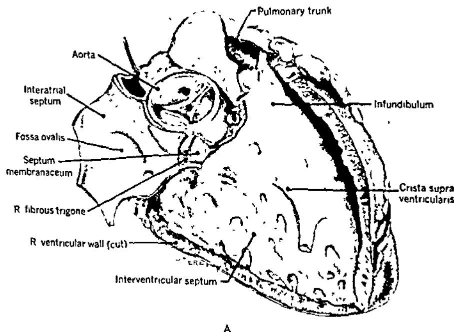
The interatrial septum, isolated by dissection, is roughly an elliptical muscular partition having its main basal fixation along a restricted sector. This basal segment is united to the remainder of the heart by a bridge of tissue lying over the line of union of the respective atrioventricular rings. The strongest point of attachment is by a narrow isthmic band from which tendinous insertions from the atrial musculature arise to connect with the right fibrous trigone and adjoining septum membranaceum (Fig. 1-20A).

A secondary zone of fixation for the atria and contained septum lies anteriorly in relation to the ascending aorta The posterior circumference of the aorta lies juxtaposed to the interatrial sulcus, forming a wide embracing atrial bay (Fig. 1-21). As a result, fusion fascia develops in the interval between the atrial and aortic walls, thus giving support to these structures as well as reinforcing the underlying interatrial septum.

Posteriorly, the interatrial sulcus is occupied by a mass of loose connective tissue containing a variable amount of fat At the crux, the junctional epicardial tissue filling the sulci makes a deep incisure under the base of the interatrial septum, so that this layer of connective tissue has a share in binding the septum with the subjacent muscular interventricular septum. The interatrial septum is fixed externally along its posterior border by the caval mesocardium, which attaches along the heart wall closely in line with the septum (Fig. 1-17B) The septum in this area is a two-leaved structure formed by duplication of left and right atrial walls which fuse along a central plane of connective tissue The laminae which

comprise this part of the septum can be easily freed from each other by dissecting in the longitudinal plane of connective tissue which extends practically as far forward as the limbus fossa ovalis Anatomically, the interatrial septum per se is, therefore, a comparatively small elliptic structure connected eccentrically to the fibrous cardiac skeleton, especially to the right fibrous trigone Although the floor of the fossa ovalis contains cardiac muscle in variable amounts, it is primarily an area of fibrous adhesion (Fig. 1-17B) between the limbus foraminis ovalis (septum secundum) and the right face of the valvula foraminis ovalis (septum primum).

The fossa ovalis has already been referred to as the *pars membranacea* of the atrial septum. This part of the septum has a pseudomembranous appearance, since it is usually well consolidated with muscle, particularly along



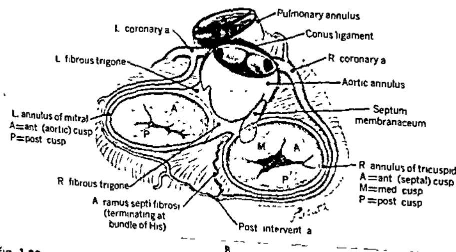
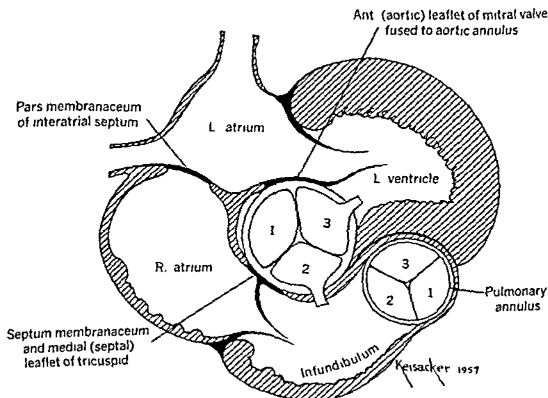


Fig. 1-20 A Diagram of septal complex shown in relief against remainder of heart Right lateral walls of heart removed. Outline of septa B. Cardiac skeleton.

its left face. The most robust muscle, *fasciculus of the septum,* however, runs peripherally around the fossa ovalis to produce the raised margin of the limbus fossa ovalis. As already stated, the strongest point of fixation of the septum to the remainder of the heart is at the *right fibrous trigone,* an area close to the region where the bundle of His issues from the atrial floor.

In comparison, when similarly freed by dissection, the isolated interventricular septum is observed to have a piriform shape The interventricular septum is conventionally divided into a small oval-shaped *pars membranacea* and a *pars muscularis,* which comprises its greatest mass. The cephalic curve of the septum is molded into a scalloped form because of the insertion of the great vessels along this margin. In over-all configuration, the combined septa have a spadelike appearance (Fig 1-20A), the interatrial septum comprising a handlelike appendage connected by a narrow restricted band to the interventricular septum.

It is significant that much of the interventricular septum is directly associated with the proximal portions of the great outflow tracts, particularly the aorta. In cross-sectional view (Fig. 1-22), the fact that the interventricular septum is predominantly an integral part of the left ventricular wall can be best appreciated. However, the septum can be roughly hemisected into a relatively thin muscular sheet belonging to the right ventricle and a thick muscular layer forming a preponderant part of the left ventricular wall. The main septal layer on the left is differentiated into a strongly developed muscular band lying below the aortic annulus. This sphincter-like *crista*



	Intact Heart	Isolated Heart
Aortic valve	1 R post	Post (noncoronary)
	2 Ant	R ant
	3 L post	L ant
Pulmonary valve	1 L ant	Ant
	2 R. ant	R post
	3 Post	L post

Fig. 1-21. Diagram showing relation of certain fibrous areas of intact heart, particularly the valves.

subaortica is particularly robust as it swings behind the pulmonary trunk anteromedially, and can be readily followed as it encircles in a less-defined fashion the remainder of the AV ostium. Thus, a robust muscular ring surrounding the base of the left ventricle is formed Its anatomic counterpart, the *crista supraventricularis*, lies on the right side and curves primarily around the base of the aorta. Pictured orthogonally, the septum musculare constitutes a central muscular axis around which the entire heart can be reconstructed In a preparation of this type, an analysis of the relationships of the respective annuli fibrosi which support the bases of the AV valvulae can be broadened (Fig. 1-17B).

The annulus of the tricuspid valve crosses the right face of the septum membranaceum, whereas the annulus of the bicuspid on the opposite side lies well above the level of the upper border of the fibrous septum from which the anterior leaflet of the bicuspid roofs over this area posteriorly. The two surfaces of the septum musculare are broken with trabeculae carneae, the left side being relatively less populated with trabeculae. In a cross-sectional view (Fig 1-22), the septum curves into the right ventricular cavity, with its concavity opening

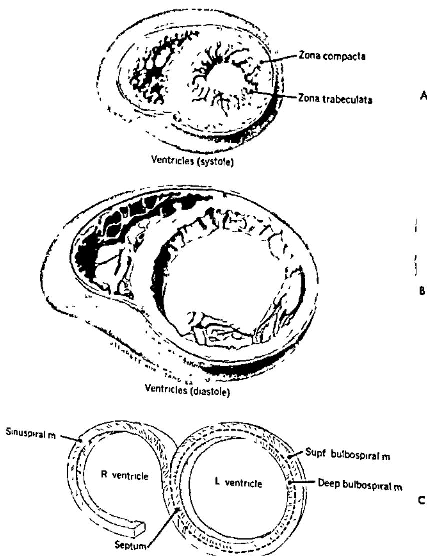


Fig. 1-22. A Cross sect- . . gram of ar . . C. Dia-

into the left chamber, clearly defining it as an architectural entity of the left ventricular wall. The anatomic apex of the heart is comprised of musculature from the left ventricular wall which forms a vortex that is equally connected to the septum. The incisura apicis cordis lies lateral to the apex, essentially along the line where the septum and right ventricular wall meet.

Valvular Apparatus. In the previous sections, it was indicated that the boundaries of transition between the primary chambers of the heart are marked by the presence of valves which serve to give the blood traversing these chambers a unidirectional flow. The valvular apparatus of the heart as a whole is reviewed in the following.

At the transition from sinus venarum to right atrium is a vestigial pair of valves, the *eustachian valve*, at the orifice of the inferior vena cava, and the *thebesian valve*, adjacent to the opening of the coronary sinus These valves are regarded as incompetent structures Throughout the remainder of the heart, two sets of physiologically competent valves operate to prevent reflux of blood from the ventricles back into the atria. Similarly, another pair of valves prohibits reflux from the great arterial trunks back into the ventricles.

Developmentally, the valve of the inferior caval orifice and the valve of the coronary sinus are derived from the right venous valve. Prenatally, the right venous valve represents a highly developed and functional structure (Fig 1-16B). Later in fetal development, this valve becomes greatly reduced in size and subdivided into two lesser vestigial structures, viz., the afore-mentioned valves of the inferior cava and coronary sinus Incomplete reduction or resorption of this valve results in formation of a lacework of tissue strands traversing the atrium, commonly referred to as a *Chiari's net*. Reticulate formations of less extensive type are more frequently encountered in relation to the valves described

The *valve of the inferior vena cava* is normally a sickle-shaped structure having its basal attachment along the free margin of the mus-

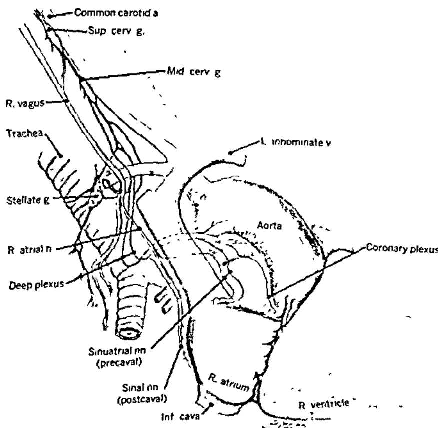


Fig. 1-23A. Right cardiac plexuses.

cular crista terminalis. The valve of the coronary sinus has a diminutive semilunar configuration and is separated from the caval valve by a fasciculus of muscle called the inferior limbic band, which is contained in the sinus septum

Valvular Function. The anatomic boundaries of the AV orifices are represented by fibrous rings separating atrial from ventricular musculature In reality, however, the effective or "functional" orifice has a funnel-shaped form (Fig 1-24), which is appreciably more restricted than the structural orifice Consequently the stream admitted from atrium to ventricle has a significantly smaller dimension from that inferred by the circumference of the annulus. In spite of the drastic alteration of the contours of the heart chambers, during each phase of the cardiac cycle, the excursion of the intervening valves is apparently surprisingly small This lack of movement of the apparatus as a whole indicates marked fixation of the cardiac skeleton and its associated structures. The free valvular edges are not permitted to ascend to the level of the plane normally described by the annulus because of the restraining effect of multiple chordae tendineae which are anchored to single- or many-headed papillary muscles. Broadly, the chordae tendineae insert at the valvular margins adjacent to the intervalvular or commissural spaces. As a result, *tendinous cords arise from more than one* papillary muscle to insert in opposing directions on adjacent valvular margins (Fig. 1-25). In this manner, the valve cusps may be drawn more completely together by tension exerted through the chordae tendineae While the ensuing traction facilitates apposition of the

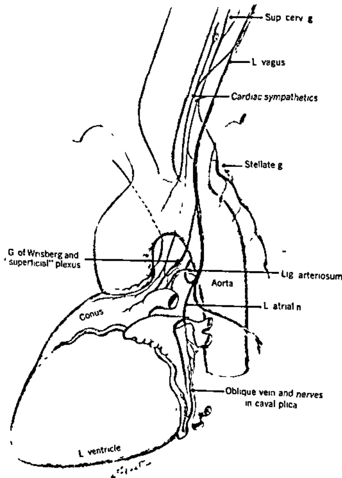


Fig 1-23B Left cardiac plexuses

cusps involved, it would appear that some minimal regurgitation must normally follow the process as physiologic necessity prior to valve closure.

Cardiac Skeleton. In addition to cardiac muscle, a series of interconnected fibrous rings (Fig. 1-20B) forms a supportive framework designed primarily for attachment of the cardiac valves. Broadly referred to as the cardiac skeleton, this system of rings is situated at those junctional levels demarcating the primary cardiac chambers and at the commencement of the roots of the arterial trunks. The cardiac skeleton is mainly composed of two pairs of fibrous rings, viz., a pair of *venous annuli* that serves to separate the atria from the ventricles, and a pair of *arterial annuli* separating the great arterial trunks from the ventricles. The former forms an almost complete partition of nonmuscular tissue, resulting in a disjunctional zone of tissue, encircling the waist of the heart, that structurally separates the atria from the ventricles. At this junctional level, identical tissues are disjoined, i.e., the cardiac musculature of the atrial wall is cut by means of fibrous tissue from that of the ventricular wall. In contrast, the cardiac musculature of the pulmonary and aortic conal outlets is separated from the smooth muscle contained in the walls of their respective arterial trunks by similar fibrous rings marking the truncoconal junctions.

ATRIOVENTRICULAR JUNCTION. The musculature of the atrial walls is disunited from the myocardial layer of the respective ventricles by a pair of conjoined fibrous rings situated at the AV junction (Figs. 1-20B, 1-27). The original cardiac muscle located here was lost prenatally through atrophy, and as a result, musculature from the atrial and ventricular walls is found inserting by tendinous slips along the lines of

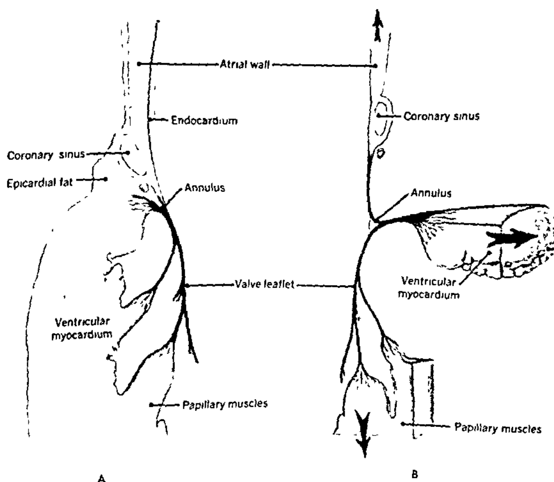


Fig. 1-24. A Histologic arrangement of AV junction. B. Fat removed from AV sulcus Junctional area stretched to show precise relations of tendinous insertions.

distribution of the fibrous skeleton. The annuli fibrosi serve primarily as supportive structures for the associated AV valves, which should be regarded as an included part of the cardiac skeleton.

The medial borders of the annuli meet along the midline over the interventricular septum immediately below the basal attachment of the interatrial septum and behind the posterior sinus of the aortic valve. At this point, the fibrous tissue is condensed into a triangular mass designated as the *right fibrous trigone* (Fig 1-20B). This trigone has special significance in that it represents the strongest single point of fixation for the elliptically shaped interatrial septum, which inserts peripherally to this fibrous mass. At the angle made by the two annuli posteriorly, the interventricular septum enters as a muscular spurlike wedge. Over this wedge-shaped area rests the interatrial septum and much of the medial floor of the right atrium, as well as the outlet conduit of the coronary sinus. It is in this locality that the *conduction bundle of His* takes origin as an insular muscular mass arising from the AV node, whence it may plunge through or bypass the trigone laterally. From here the bundle takes a course to skirt the crest of the interventricular muscular septum.

The naming of the leaflets of the AV valves is fairly constant. The bicuspid valve is generally regarded as composed of an *anterior leaflet* and a *posterior leaflet*. The tricuspid valve, on the other hand, is made up of *anterior, medial*, and *posterior leaflets*. The valvular apparatus in each case can be simply regarded originally as a single continuous diaphragm of fibrous tissue slit centrally to form two or more dependent parts that open freely into the ventricular cavity. Within the ventricular cavities, the valve leaflets are anchored by tendinous cords (*chordae tendineae*) to the muscle columns of papillary muscles, already described in detail. The basal attachment for the leaflets is at the annulus fibrosus. In this fashion, all the component leaflets are united circumferentially by a shelf of valvular tissue, called the *commissures*. The commissures are located at the *intervalvular spaces*, thereby completing an interconnected cufflike fibrous

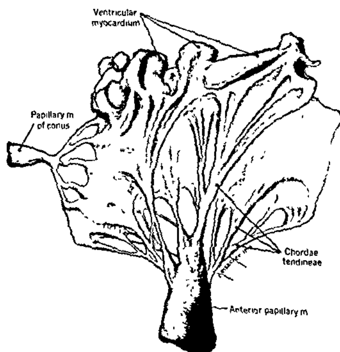


Fig 1-25A. Inferior surface of anterior leaflets of tricuspid valve. Anterior papillary muscle and myocardium from ventricular wall retained.

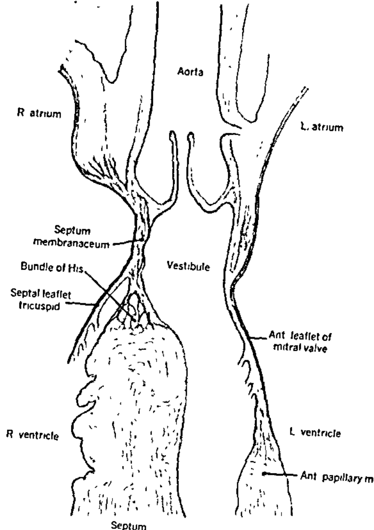


Fig. 1-25B. Histologic organization of heart in region of septum membranaceum and anterior leaflet of mitral valve

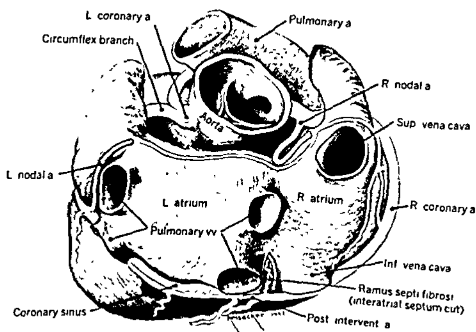


Fig. 1-26. Posterior view of heart viewed from above to show branches of coronary arteries

band surrounding the AV orifice. Variations in the number and configuration of the valvular leaflets are frequently encountered, resulting most commonly in formation of *supernumerary intermediate cusps* at the locations of the commissures These intercalated leaflets, sometimes called *accessory* or *commissural leaflets*, are fixed in position by either a directly associated group of chordae tendineae or by secondary branchings from the chordae tendineae belonging to adjoining leaflets. Reduplication of the mitral orifice is sometimes (rarely) encountered as a morphologic variation from the normal

SEPTUM MEMBRANACEUM Viewed from the left ventricle, the septum membranaceum is an oval-shaped fibrous plaque that seals the so-called "undefended" space situated directly above the crest of the muscular interventricular septum (Fig 1-17B). An apical part of the membranous septum extends upward to become lodged bet[illegible] l posterior [illegible] to its re- [illegible] 17B), the septum membranaceum lies internally *or medially* to the parietal band of the crista supraventricularis and is located subjacent to the line of attachment of the medial leaflet of the tricuspid.

Because of the angulation of the right venous annulus, the base of the medial valvula is brought into direct relation with the right face of the septum membranaceum and is normally found draped across part of the fibrous septum (Figs. 1-17B, 1-25A). This leaflet frequently becomes partly adherent to the septum along its basal border. In this manner the septum membranaceum is transected into two parts by the valve (Fig 1-25A). The upper half represents a fibrous AV partition separating the right atrial cavity and the left ventricle. The lower half lies interposed between the two ventricular cavities and is regarded as its pars interventricularis Consequently, a variety of septal defects occurring at this favored site, in conformity with the anatomy in this area, results in at least three main types of high ventricular septal defects an AV *fistula* a defect [illegible]

[illegible]

The mode of attachment of the medial leaflet of the tricuspid to the septum is variable, resulting in equally modified segmentation of the membranous septum Along its posterior margin, the septum membranaceum has an attachment to the right fibrous trigone. The right wing of the atrial bay is fused with the aortic wall above this area and is markedly thin. When the atrial wall is freed from this part of the aorta, the apicalward extension of the fibrous septum to the level of the right aortic commissure can be clearly seen. For this reason interventricular septal defects can be sufficiently extensive to cut as high as the commissure of the aortic valve.

TRICUSPID VALVE. The remainder of the cardiac skeleton is completed by the AV valves and their respective annular zones of attachment. As the name *implies, three leaflets* comprise the tricuspid valve (Figs 1-16, 1-20B), viz, anterior, medial, and posterior valvulae. The *anterior leaflet* (cuspis ventralis) of the tricuspid valve has its basal attachment to that part of the annulus reinforced inferiorly by the parietal band of the crista supraventricularis. The anterior leaflet arises from the sternocostal *segment* of the annulus and comprises a well-developed membrane that partially partitions the ventricular cavity in a fashion similar to its counterpart in the left cavity. The chordae tendineae serving to anchor the leaflet in position arise mostly from a robust muscular mass *that* springs from the ventricular wall, called the anterior papillary muscle.

As previously described, the base of the *medial cusp* (cuspis septalis) takes its origin along a line of attachment which bears a primary relationship to the septum membranaceum The precise line of attachment of the valve to the fibrous septum is exceedingly variable. It lies at a level somewhat lower *than* the attachment of the anterior cusp of the *bicuspid* on the opposite side (Fig. 1-17B). The chordae tendineae anchoring the medial or *septal leaflet* arise, for the most part, from papillary muscles situated along the septal *wall* The anterior and medial valvulae form an archway so that the venous return must curve in order *to enter the* conus arteriosus which represents the outflow tract of the right ventricle

The *posterior leaflet* (cuspis dorsalis) is less strongly developed than *its two* companion valvulae and springs from that part of the

annulus immediately adjacent to the atrial floor. The chordae tendineae normally associated with this valvula arise from a number of small papillary muscles situated along the ventricular floor. In addition to the valves described, supernumerary leaflets can frequently occur at the intervalvular spaces.

MITRAL VALVE. The bicuspid, or mitral, valve is composed mainly of an anterior and a posterior cusp (Figs. 1-17A, 1-20B). In addition to the named leaflets, accessory leaflets are frequently encountered at the commissures. Corresponding anterior and posterior groups of papillary muscles serve to anchor the leaflets within the ventricular cavity by way of chordae tendineae which insert primarily along the free margins adjacent to the intervalvular spaces. Contributions of chordae tendineae from both anterior and posterior papillary muscle groups are distributed to each respective leaflet.

The *anterior leaflet* (cuspis anterior) has a double fibrous attachment. In addition to arising from the left AV annulus, the base of the leaflet is partly united with the posteriorly directed segment of the aortic annulus The "lie" of the anterior leaflet is such that it appears to hang centrally into the ventricular cavity in the manner of a curtain-like partition Because of its union with the fibrous ring of the aorta, the anterior leaflet is sometimes referred to as the *aortic leaflet*. Unlike the anterior cusp of the tricuspid, the anterior leaflet of the mitral possesses no reinforcing band of muscle homologous to the thick mural band of the crista supraventricularis The intermediate portion of the composite septum formed by the union of the aortic annulus and the anterior leaflet is fused with part of the anterior wall of the left atrium (Fig 1-17). A reinforcing fusion fascia develops in the intervening potential space between the atrial wall and "septum"

The *posterior cusp* (cuspis posterior) is less strongly developed than its companion and exceedingly more variable. This leaflet of the bicuspid takes its origin from that limb of the left annulus situated in the plane below the coronary sinus. When the commissural areas between the leaflets contain *accessory lesser cusps*, the valve assumes a sleevelike form when regarded as fully extended into the ventricular cavity.

If the left atrial wall is freed from its zone of fusion with the aortic annulus, it can be seen that a fibrous membrane, or lamina affixa, extends below the level of the annulus as far as the basal attachment of the anterior cusp of the bicuspid. Followed forward, the annulus becomes condensed adjacent to the base of the left anterior cusp of the aorta to form a second fibrous triangle called the *left fibrous trigone* (Fig 1-20B). In some respects, the membranous portion of the aortic wall described and the manner in which the anterior leaflet takes origin from this area are homologous to the relationship of the septal cusp of the tricuspid and the septum membranaceum.

CONOTRUNCAL JUNCTION. Histologically the conotruncal junction represents a line of transition between dissimilar tissues. Two such junctions exist, one at the commencement of the aorta from the left ventricle and another at the level where the pulmonary trunk meets the conus on the right. In each case, the smooth muscle of the media of the aorta and the pulmonary trunk is separated from the cardiac muscle of the respective ventricle.

Below the level of the pulmonary valve, the conal wall is markedly thin as it lies against the aorta. In cross section, the wall of the conus has a crescentic configuration, with its thin segment forming the floor of the infundibulum while its more muscular segment forms the free wall lying anteriorly When the wall of this transitional zone is examined, slips of cardiac muscle may be found extending upward for some distances to pass into the adventitia of the pulmonary trunk. Rich plexuses of nerves with their associated ganglia may be found in the connective tissue subjacent to the infundibular floor

In the case of the aorta, the histologic transition is more pronounced. In addition, the insertion of the aorta flares quite markedly over the thickened basal margin of the left ventricular wall Here, also, scanty strips of cardiac muscle may be picked up lying within the adventitia of the aorta.

AORTIC VALVE The isolated left ventricle has a truly conical configuration Although the aorta arises cylindrically from the left ventricle, it lies centrally with reference to the heart as a whole The aortic valve lies at the commence-

ment of the stemlike aorta and is comprised of three semilunar valvulae (Fig 1-17A) which bend to open into the aortic outlet.

The terminology employed in the nomenclature of the semilunar valves depends upon two sets of conditions, i e, the naming of the valvulae varies according to whether the heart is removed from the body or is lying in situ within the thorax. In the anatomically intact heart (Fig. 1-21), the terminology is based upon the positions of the valves relative to the main body axis According to this system, the aortic valve consists of one anterior cusp, plus left and right posterior cusps At the midpoints of the free margins of the valvulae are located fibrocartilaginous nodules, called the *noduli Arantii*.

In the isolated heart (Fig 1-20B), an entirely different nomenclature is employed. According to this system, the heart is so oriented that the plane of the interventricular septum represents the main axis of the organ, with the aorta and pulmonary trunk lying dorsally and ventrally with respect to each other On this basis, the aortic valve *is composed of one posterior (noncoronary) cusp* plus *left* and *right anterior (coronary) cusps* Similarly, the valve of the pulmonary trunk possesses one *anterior* plus *left* and *right posterior cusps.* In all cases, the terms posterior and anterior are commonly employed although the terms dorsal and ventral are more pertinent when discussing structures in relation to the entire body

The wall of the aorta adjacent to each valve cusp is contoured by dilatations (Fig. 1-18) corresponding to the *aortic sinuses (of Valsalva)* The sinal walls of the aorta bulge outward well beyond the limits of the aortic annulus A right anterior dilatation projects into the thin-walled infundibulum, whereas a posterior dilatation swells back over the interventricular septum and forms a distinct promontory which abuts against the medial wall of the right atrium A left anterior dilatation is directed against the pulmonary trunk as it wraps around the aorta.

The function of support for the aortic trunk is ascribed to a fibrous annulus situated at its insertion into the left ventricle The aortic annulus marks a conotruncal junction representing a structural transition from cardiac to smooth muscle Unlike the AV annuli, the aortic annulus is not a well-defined fibrous ring. In place of a discrete annulus, the transitional zone in question is distinguished by a wide fibrous membrane encircling the base of the aorta and hanging somewhat below the inferior borders of the aortic sinuses In addition, the fibrous membrane crosses the intervalvular gap between the dilatations marking the aortic sinuses In these areas, the membrane has a triangular form, having its apex interposed between the bases of the valvulae at the level of the commissures Three similar fibrous plaques occupy these intervalvular spaces, which lie below each commissural level Of the three, the membrane lying anteriorly between the right and left valvulae is least membranous, being the thicker and more fibrous member. The latter membrane is a derivative of the original aortic septum which partitions the truncus arteriosus prenatally into the aorta and the pulmonary trunk The left commissural membrane is extensively connective with the anterior leaflet of the bicuspid valve, whereas the right commissural membrane, lying between the right anterior and posterior cusps, is of *special significance*, since it is directly associated with the septum membranaceum, as previously described.

PULMONARY VALVE. The pulmonary valve is composed of three semilunar valvulae In the *isolated heart* these valvulae are designated as one anterior plus paired right and left posterior cusps (Figs 1-16, 1-20B) According to the method of naming employed in the anatomically intact heart, the valve consists of *one posterior cusp* plus *left* and *right anterior cusps* (Fig. 1-21). Sacculations comparable to the aortic sinuses contour the wall of the pulmonary trunk adjacent to the level of the pulmonary valve. These dilatations are not so prominent as those found in the aorta, and the wall of the pulmonary trunk with its contained valve is generally less strongly developed. *Fibrous nodules* similar to the noduli Arantii occur at the midpoints of the free margins of the cusps

The pulmonary trunk wraps around the base of the aorta, reaching this area as a direct continuation of the infundibulum. The contiguous walls of the two vessels are markedly thin along their plane of apposition Bridging the interval between the annular insertion of the aortic root and that of the pulmonary trunk

may be found a fibrous band called the *conus ligament.* The conus ligament is actually part of a fibrous sheet of compressed fusion fascia formed in this interval and extends from the aortic wall adjacent to the right anterior sinus to pass laterally where it blends with the adventitia of the left side of the pulmonary trunk. The right flow tract is inclined somewhat horizontally in relation to the aorta, and as a result, the right venous annulus is rotated roughly at a right angle to the main axis of the ascending aorta. The pulmonary valve is less angulated and describes approximately half the former angulation with the aortic valve. In contrast, the left venous annulus lies essentially in the same plane as the aortic valve.

Within the right atrial wall, a small ligament passes from the point where the valve of the inferior vena cava meets the valve of the coronary sinus. This tendinous slip passes deep into the septal wall to run part way within the anterior pillar of the fossa ovalis Called the *tendon of Todaro,* it terminates by having a partial insertion into the underlying right fibrous trigone. Additional ligamentous bands may be found at various other points of the atrial wall. These ligaments fall collectively into the category of structures classified under cardiac skeleton

Muscular Architecture. Examination of a ventricle in cross section (Fig 1-22) reveals the heart wall as consisting of two basic subdivisions, viz., an *outer compact zone* and an *inner trabeculated zone* The zones in question are composed of syncytially arranged muscle layers. Analysis of the organization of cardiac muscle concerns itself chiefly with dissection of the compact stratum The over-all thickness of the left ventricular wall is characteristically greater than that of the right, the compact layer in this case being proportionately thicker than the underlying trabeculated layer The reverse is true for the right ventricular wall, where the trabeculated zone exceeds the compactum in depth. The muscular *interventricular septum* is the thickest part of the heart structure, comprising essentially a duplication of the right and left wall masses, but differs by being trabeculated on both sides.

Anatomically, the septum functions predominantly as an integral structural unit of the left ventricle. It is obvious, from the syncytial character of the muscle wall, that precise connective tissue planes could be ascribed only to the compact zones of the heart wall. Nevertheless, the perimysial planes pertaining to these compact layers are ill defined and consequently extremely difficult to follow. The heart musculature appears to be arranged in sheets which in general spiral inward from superficial levels The fibers of the superficial layers run at right angles to those of the deeper layers. The syncytial arrangement of the structural units is generally conceded and complicates attempts to unravel these muscle layers into their component parts. In addition, it has been recognized that the torsion process the heart undergoes developmentally during the stage of cardiac loop is a contributing factor preventing complete regular lamination. The general organization of the heart musculature is in two principal layers, viz , *superficial* and *deep.* The layers in question take their origin from the tendinous layers comprising the fibrous base of the heart and terminate by reinserting along different points of the same cardiac skeleton

The right ventricular wall is easily separated from the septal wall along its anterior margin, and the muscle layer thus freed can be traced posteriorly into the main mass of the septum Similarly, the left ventricular wall can be separated from the posterior border of the septum In contrast, the left ventricular musculature can be followed as a spiral that enters the main septal mass anteriorly. Unrolling the heart musculature in this manner reveals that it is arranged in two major scrolls coiled in essentially the same direction The ventricular scrolls unroll counterclockwise from their attachment to the septum.

There is fair agreement among most investigators with regard to the architecture of the superficial stratum of muscle A *superficial bulbospiral (aortospiral) group* arises from the left half of the cardiac skeleton. As the name implies, this muscle arises in part from the aortic annulus and, passing to the margo obtusus, spreads posteriorly over the diaphragmatic surface to end as muscle columns at the bases of the posterior papillary muscle groups in relation to the bicuspid and tricuspid valves, respectively In contrast, a *superficial sinospiral layer* arises around the orifice of the right venous inlet from which it radiates to cover most of the sternocostal surface of the right ventricle. This muscle receives its name from

the fact that this opening is directly associated with the sinus portion of the heart Both muscle groups ultimately converge toward the apex, forming *muscular vortices* in the form of anterior and posterior horns that enter the ventricular walls as muscular columns, finally projecting into the cavities as papillary muscles.

The definition of the deeper layers of the myocardium is less precise and not clearly ascertained An intermediate or "middle layer," called the *deep sinospiral muscle*, encircles both ventricles after having taken origin to a great extent from the left annulus Fibers from the deepest layer of this muscular band penetrate the septum along the posterior interventricular sulcus The deep sinospiral muscle is apparently incomplete, since it becomes fenestrated by wide deficient areas toward the apex The most deeply situated muscular layer on the left is represented by a robust *deep bulbospiral muscle* that takes its *origin from the* septal circumference of the left venous annulus and to which it *returns from insertion* This layer is confined [illegible]

spiral and sinospiral muscles interlock upon reaching the septum musculare.

The *interventricular muscular septum is* constructed by a meshing of the muscular groups from the two sides, predominantly that *of the* left wall A connecting *interpapillary* group of fasciculi lies inferiorly, crossing *the septal* wall near the apex

The musculature of the atrial walls may be similarly subdivided into *superficial* and *deep layers* The superficial layer of the atrial wall has a relatively simple distribution, consisting essentially of ribbon-like bands encircling both atria. The *deep* layer is most strongly developed, particularly in the right atrium In this chamber *the* deep layer consists of muscular loops encircling the venous inlets Most prominent in this category is the *crista terminalis* (Fig 1-18), which borders the superior and inferior caval orifices laterally The *limbus fossae ovalis* should *also be* included in this classification, since it represents a muscular ring that developed around an embryonic type of venous orifice, the foramen ovale, which is obliterated postnatally. From the crista terminalis arise the *ribbon-like musculi pectinati*, most of which terminate by inserting at the right fibrous ring, while others pass comb-fashion into the auricular appendage where they become reorganized into muscular trabeculae.

In contrast, the left atrial wall (Fig 1-17) consists essentially of a single muscle layer presenting a smooth atrial surface internally. In the region of the auricular appendage, the musculature forms trabeculations similar to those of the right atrial wall. Muscular contributions from both atrial walls form the interatrial septum. The musculature of the left atrium completely encircles the adventitia of the coronary sinus but is gradually lost at the entrances of the pulmonary veins. Membranous areas of the atrial wall, apparently deficient in myocardium, are frequently *encountered in* both atrial walls and may be clearly mapped by transmitted light. However, most of these areas contain a reduced myocardial layer which can be *observed histologically*.

The *interatrial septum* is constructed to a great extent by invagination of the adjacent atrial walls posteriorly, thus forming a central connective tissue plane The muscular fasciculus encircling the limbus foraminis ovalis is comprised of a *superior limbic band* contained in the anterior pillar and a *posterior limbic band* which runs in the posterior pillar. The *crista interveniens* is a lateral extension of the superior limbic band which forms a raised margin across the wall of the sinus venarum internally These muscular bands chiefly operate to maintain the venous orifices sufficiently wide to ensure maximum filling of the atria

Cardiac Innervation. Neurologic control of the heart action is mediated through two sets of paracervical nerve plexuses representing *parasympathetic* and sympathetic divisions of the autonomic nervous system. From these plexuses, cardiac branches descend into the *mediastinum* to enter into superficial and deep cardiac plexuses. The terms "superficial" and "deep" have been adopted as a matter of convenience but carry no anatomic preciseness of meaning. *The parasympathetic component* consists of cardiac branches arising from the vagus nerve, whereas the main sympathetic elements take origin principally from that portion of the *sympathetic* trunk lying at cervical levels. *The deep* cardiac plexus, in particular, has been variously described in position. However, this plexus is in most cases situated along the right

side of the distal end of the trachea above the level of the bifurcation, whereas the superficial cardiac plexus is found nestling under the aortic arch The two plexuses are interconnected. An attempt has been made to unravel the plexuses involved into their component parts.

Description of the cardiac innervation is given a more functional connotation if, in addition to dissection of the paracervical nerve plexuses, the cardiac nerves are freed at their termination in the heart wall and then traced back to their particular plexus of source In this manner, individual nerves can be carefully followed through the intermediate plexuses to their points of origin from the main trunk of origin. By relating specific cardiac branches to particular zones of the heart, a precise anatomic definition is given to the cardiac branches of the vagal and sympathetic trunks.

The *cardiac nerves* utilize the dorsally situated mesocardia as avenues of entry into the heart wall (Fig. 1-14B) The mesocardia are formed by duplicated reflections of the pericardium, comprising double serous supporting membranes for the heart. Two principal sets of mesocardia serve for attachment of the heart. One set lies at the venous, or sinoatrial, end embracing the venous inlets into the atria, thus giving rise to a venous, or sinoatrial, mesocardium. Another set invests the great arterial trunks as they leave the heart to form an arterial, or conotruncal, mesocardium Contained within the two leaves of these membranes are the cardiac nerves, which reach the heart wall from the mediastinum to produce the above plexuses.

The arterial and venous mesocardia are separated by the transverse pericardial sinus but are reunited along the mediastinal wall dorsally. This mediastinal area forms a promontory overlying principally the thoracic aorta and pulmonary structures contained within the posterior mediastinum. As the cardiac nerves reach this zone, they diverge into one set that passes over the upper border of the transverse pericardial sinus (to end around the roots of the aorta and pulmonary trunk) while another set passes under the lower margin of the sinus (to terminate along the atrial walls and associated veins).

In general, the cardiac nerves are arranged in plexuses around the major vascular trunks associated with the heart and, as a result, can be classified into two broad plexuses. An *arterial plexus* exists in relation to the great arterial trunks as they leave the heart, principally the aorta, whereas the *venous plexus* is found in relation to the heart where the great veins open into the atria. In each case, both vagal and sympathetic branches are represented.

THE ARTERIAL CARDIAC PLEXUS. Prenatally, alteration of the blood vascular picture in the attainment of the definitive arterial pattern favors the retention of the main arterial routes on the left of the heart and a dropping out of those on the right. During development, the primitive left fourth and sixth aortic arches are retained to give rise postnatally to the arch of the aorta and the ductus arteriosus, respectively For this reason, the cardiac branches arising off the left vagus and those from the cervical sympathetic trunk of the same side are carried into primary relationship with the aortic arch, with the ligamentum arteriosum, and the pulmonary trunk. With left arterial dominance, the arch of the aorta and its branches become linked with the left cervical cardiac plexus, thus forming an *arterial or conotruncal (bulbar) plexus* The pulmonary trunk and the ligamentum arteriosum become equally involved in this complex process of evolution, reflecting the transition of the arterial picture from prenatal to postnatal conditions

THE VENOUS CARDIAC PLEXUS In contrast to left arterial dominance, the reverse picture holds for innervation of the sinoatrial end of the heart A shift to the right occurs prenatally in the establishment of the venous circulation. That is, a right superior vena cava is retained at the expense of its embryonic homologue, the left horn of the sinus venosus, which progressively drops out of the picture as a potential left superior cava Concomitantly, the sinus venosus is displaced from its original midline position in order to enter the right atrium As a result, the venous end of the heart becomes predominantly associated with the cardiac nerves arising from the right cardiac plexus. However, the oblique vein of the left atrium, a vestige of the embryonic left superior vena cava, continues to retain its original relationship to the left vagus and associated sympathetic fibers Consequently, a venous, or sinoatrial, plexus is formed around the great veins and atria

THE RIGHT CARDIAC PLEXUS The *parasympathetic division* of the autonomic nervous system is represented by cardiac branches which arise from the vagus The principal cardiac branch from the vagus is given off at the level where the right recurrent laryngeal nerve forms a loop to curve under the subclavian artery In Fig 1-23A, this nerve is designated as the right atrial nerve. From this point, it descends into the posterior mediastinum, where it passes immediately anterior to the right bronchus and pulmonary artery, in front of which it soon breaks into secondary branchings that terminate in the heart wall

The direct continuation of the right atrial nerve is represented by a sinal, or postcaval, branch, which runs within the caval mesocardium, coursing dorsally in relation to the sinus venarum Mural filaments leave this sinal branch periodically *to terminate in the interatrial* septum and the crista terminalis In its lower extent, the right sinal nerve ends in relation to the inferior caval orifice. At the level of the base of the *interatrial septum*, deeply penetrating twigs reach the floor of the left atrium *to innervate the conducting elements of the AV node and bundle*. Terminal ganglion cells are strewn along the atrial wall at the points of penetration of these filaments.

A precaval branch runs deep within the adventitia of the superior vena cava, coursing around the medial aspect of the caval *insertion* From this point, it cuts laterally across the atrial roof to plunge finally into the tissue of the SA node The nerve in question is designated as the *sinoatrial branch* Prior to the point where this branch penetrates the heart wall, it enters a large *ganglionic mass (ganglion of Aschoff)* that lies deeply embedded in the atrial wall at the mural attachment of the caval mesocardium.

The *sympathetic division* of the cardiac innervation gives rise to similar postcaval and precaval nerves which closely accompany the afore-mentioned vagal branches (Fig 1-23A). The sympathetic cardiac branches contribute strongly to left and right coronary plexuses In contrast to the vagal branches, the right sympathetic cardiac branches are reconstituted over the distal segment of the trachea into a plexus lying somewhat above the level of the bifurcation This plexus, referred to as the "*deep" cardiac plexus*, is composed predominantly of sympathetic cardiac branches arising from the right sympathetic trunk and is intricately intermingled with the nerves that enter into the pulmonary plexuses Above the thoracic aperture the cardiac sympathetic branches ascend into the neck, where they join the cervical sympathetic trunk.

Three sympathetic branches may be normally followed at cervical levels. An inferior cardiac branch leads into the *inferior cervical ganglion* (Tandler). When it is present, a middle cardiac branch can be traced into the middle cervical ganglion This nerve may sometimes enter a smaller ganglionic mass called the *middle cardiac ganglion* (*of Arnold*). The nerves described correspond respectively to the parasympathetic caval branches and nerves of the coronary plexus discussed above. A superior, but inconstant, cardiac branch may arise from the superior cervical ganglion of the sympathetic trunk to connect directly with the vagus or join the superior laryngeal nerve prior to descending into the neck When present, this nerve may sometimes terminate in a small ganglionic mass near the aorta called the *superior cardiac ganglion (of Valentine)*. Tandler also described a *cardiac nervus imus* which occasionally connects with the *first thoracic* (or *stellate*) ganglion and is identical to a *fourth cardiac nerve* (*of Valentine*), when present.

THE LEFT CARDIAC PLEXUS On the left side, the *principal vagal branch* to the heart wall arises from the main trunk below the level of the recurrent laryngeal nerve, where it curves under the ligamentum arteriosum and aortic arch From this point, this cardiac branch, designated as the *left atrial nerve* (Fig. 1-23B), exits from the mediastinum to enter the caval *plica* In its course through the plica, nerve filaments fan out medially over the *left* atrial wall posteriorly to become associated with the widely scattered terminal ganglia found here, *particularly* over the region of the coronary sinus. Within the plica, the left atrial nerve bears a primary relationship to the contained *oblique vein of Marshall*, which is the vascular rudiment of the embryonic left superior vena cava (*left horn on the sinus venosus*). In cases of persistent left superior cavae, this nerve is observed to be as well developed as its homologue on the right. Because of the richness of nerves it contains, the caval fold is sometimes referred to as the "*plicae nervinae*"

A *preaortic (inferior cardiac) vagal branch* crosses the aortic arch in the region of the ligamentum arteriosum. However, the preaortic branches may be more than one in number. The nerves contained within the aortic recess and those that overlie the aortic arch collectively comprise the *superficial cardiac plexus.* Medial to the ligamentum arteriosum one finds an inconstant diffuse ganglionic mass (the *ganglion of Wrisberg*). The preaortic nerve is frequently in anastomotic union with the cervical sympathetic trunk.

The *left set* of sympathetic cardiac nerves includes branches bearing a direct relationship to the great arterial vessels, particularly the aortic arch. The main sympathetic nerve is represented by a branch which courses in the interval between aorta and pulmonary trunk, passes medial to the ligamentum arteriosum. and then swings postaortically under the arch to ascend into the neck, where it lies as a direct continuation of the cervical sympathetic trunk. An additional postaortic sympathetic branch usually accompanies the main cardiac nerve, arising from the vagus to enter the caval plica Two fairly constant preaortic branches may also be found terminating in relation to the arch.

Conventionally, *three sympathetic cardiac branches* are described leaving the sympathetic trunk at cervical levels. A left superior cardiac branch from the sympathetic trunk on the left joins the inferior cardiac branch from the vagus to enter the superficial cardiac plexus The superior cardiac nerves in both cases are less constant in origin. Cardiac branches which leave the main sympathetic trunk at thoracic levels are primarily nerves that terminate in the wall of the aorta Some filaments, principally from the stellate ganglion, ascend into the postaortic nerves.

The *sympathetic trunk* in the neck is complex in its interconnections. Although the superior and inferior cervical ganglia are fairly constant in position, the intermediate segment of the trunk is extremely variable. The *middle cervical ganglion* is variously situated in relation to the inferior thyroid or vertebral arteries The interconnections of the middle cervical ganglion with its associated ganglia are particularly intricate The *inferior cervical ganglion* is frequently fused with the first thoracic ganglion to form the *stellate ganglion.* An *intermediate,* or *vertebral, ganglion* may sometimes be present. The vagal and sympathetic cardiac branches sometimes become indistinguishably united to form a single trunk. In these cases the nerves in question are designated as vagosympathetic cardiac branches. For the most part, the cardiac nerves described in the foregoing discussion are confined principally to the atrial and arterial walls. However, *some neural filaments reach the ventricular walls* by spreading subepicardially, particularly along the routes of the coronary vessels and their branches. Evidence of fibers filtering deeply through the myocardial wall is suggested by the presence of delicate nerve meshes occasionally encountered under the endocardial lining.

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A similar, less constant, ganglion is lodged within the subaortic recess to the right of the ligamentum arteriosum This *ganglion of Wrisberg,* as it is called, is composed of multipolar cells similar to those found in the cervical sympathetic trunk The supporting stroma is less compact and abundant in lymphoid tissue. In general, the cardiac ganglia possess a rich vascularity Functionally, the cardiac ganglia should be regarded as a neurovascular tissue representing integral units of the cardiac conduction mechanism, essential for the maintenance of the excitation wave

5

Histology of the heart

General Histology

RICHARD H. LICATA

The Conduction System

JOSEPH THOMAS ROBERTS

GENERAL HISTOLOGY

GENERAL ORGANIZATION OF CARDIAC TISSUES

Although paired cardiac chambers are histologically separated at the AV junction, the members of each pair are mutually united by cardiac muscle at the septa. As a result of this muscular linking, the paired atria and ventricles, respectively, function in unison. Architecturally, the structural organization of the heart varies according to the individual chamber. In particular, marked differences exist in the general arrangement and amount of muscle present in the cardiac walls.

In general, the heart wall is regarded as composed of three basic layers, viz., an outer investing serous layer called the *epicardium* (visceral pericardium), an inner endothelial lining called the *endocardium*, and an intermediate muscular layer, or *myocardium*, which comprises the bulk of the wall thickness. In comparison with those of the *ventricles, the* walls of the atria are membranous. Internally, the right atrial musculature is arranged in ribbon-like fasciculi (taeniae musculares) that arise laterally from the crista *terminalis and* fan out in wide loops toward the AV annulus. These fascicles, viz., the *musculi pectinati atriorum*, regroup to converge finally on the auricular appendage, where they break into a number of irregular trabeculae similarly referred to as *musculi pectinati auriculorum*. The *atrial wall* on the whole is relatively weakly compacted with myocardium. The intermediate areas, alternating with the muscle bundles, are sometimes deficient in muscle fibers. The wall of the *right atrium* in these locations consists almost solely of duplicated epicardial and endocardial layers which as a rule enwrap minimal amounts of cardiac muscle. Conversely, the *left atrial wall* is relatively more homogeneous in its distribution of muscle tissue and, in some cases, contains wide membranous areas, owing to local reduction of the muscle layer.

Muscle fascicles arise from the atrial musculature, which is described as spiraling for variable distances within the adventitia of the entering veins. A prominent investing layer of cardiac muscle is present at the root of the *superior vena cava* near its orifice (specifically designated as *Wenckebach's bundle*). The wall of the coronary sinus, unlike that of its venous branches, receives a complete adventitial investment of cardiac muscle. This tunic extends as far as the proximal segments of the cardiac veins. It is obvious that the sinus should, therefore, be regarded histologically as a corporate part of the left atrium.

The walls of the *ventricles* are similarly subdivided into epicardium, myocardium, and endocardium. Structurally, the myocardial layer can be further divided into two secondary parts, viz., an inner *trabeculated zone* and an outer *compact zone*. The trabeculated zone of the right chamber is proportionately thicker than its overlying compact muscle layer. In contrast,

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A similar, less constant, ganglion is lodged within the subaortic recess to the right of the ligamentum arteriosum. This *ganglion of Wrisberg,* as it is called, is composed of multipolar cells similar to those found in the cervical sympathetic trunk The supporting stroma is less compact and abundant in lymphoid tissue In general, the cardiac ganglia possess a rich vascularity. Functionally, the cardiac ganglia should be regarded as a neurovascular tissue representing integral units of the cardiac conduction mechanism, essential for the maintenance of the excitation wave.

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cle of the aorta and pulmonary trunk. The line of union of the walls of the *sinus venarum* and right atrium may be regarded as a third transitional zone. Here, the precise line of juncture is ill defined, the original muscular unity of the embryonic sinus venosus and atrium having been preserved postnatally.

Atrioventricular Junction. The general architecture of the AV junction is greatly obscured by external accumulations of epicardial fat lodged within the corresponding sulcus. In cross-sectional view, the epicardial fat appears as a wedge which cuts deeply into the wall of the junctional zone (Fig 1-24A). However, if the epicardial tissue normally filling the sulcus is removed, the organization of this area can be more fully appraised.

Conotruncal Junction. An ill-defined sulcus marks the junctional zone separating the ventricular chambers from their respective arterial vessels. The annuli fibrosi found in these locations comprise in reality fairly wide but irregular fibrous bands. The sulcus at the level of the conopulmonary junction (*fretum Halleri*) is covered by a thick epicardial layer containing a fair amount of adipose tissue. Since the aortic root lies deeply embedded in fusion fascia, the sulcus that would normally correspond to the aortoventricular junction is hidden from view.

Infrequently, scant slips of cardiac muscle can be traced beyond the fibrous rings, penetrating the adventitia that invests the walls of the great arteries.

When a block specimen is obtained from such an area and fixed in a stretched condition, the precise junctional zone is seen arranged as a cuff at these levels and contains minimal amounts of atrophied muscle elements. Less commonly, muscle fibers similar to Purkinje fibers of the conduction system are encountered in this location. The tendinous material comprising the arterial annuli shows the typical muscle tendon arrangement. For example, collagenous bundles arising from the tendons at the junction enter the endomysium surrounding the ventricular muscle. As before, some of these collagenous fibers insert into the sarcolemma while others penetrate the core of the individual muscle cell.

The relationship of the structures comprising the junctional wall can be clearly observed. In such a preparation, three ligamentous bands can be demonstrated converging at the atrioventricular junction (Fig 1-24B). A superior band represents the basal insertion of tendons arising from the atrial musculature. A second band extends into this zone as a direct continuation of the tendinous lamina of the associated valvular apparatus. A third, and by far the most developed tendinous band, arises inferiorly from the ventricular wall. The *annulus fibrosus* is thus formed at the point where the three fibrous bands meet. The annulus, therefore, is a composite mass resulting from the bands described, and is usually altered in position in the intact heart because of the presence of variable amounts of epicardial fat.

HISTOLOGIC ANALYSIS OF THE CARDIAC SKELETON

Annulus Fibrosus. Histologically, the AV junction consists predominantly of collagenous tissue embryonically derived from two different sources. One of the fibrous components is tendinous in nature, having arisen as a result of hypogenesis of the original muscular link which prenatally connected the atrial and ventricular walls. The annulus fibrosus and its associated ligaments are the fibrous vestiges of cardiac muscle that underwent atrophy during the developmental process. The remainder of the collagenous tissue found at the junctional zone is primarily a packing tissue comprised of fine fibers similar to those found in the endocardial and epicardial layers. In contrast to the tendinous bands, the fibrous packing tissue is derived from a layer of the embryonic heart referred to as *endocardial cushion tissue*.

Histologically, the annulus fibrosus is com-

...sue are experimentally treated with digestive enzymes, such as *collagenase*, the constituent fiber bundles of the annulus are readily loosened from each other. In preparations of this type, the coarse collagenous bundles splay out into tuftlike cords. Under these conditions, it can be observed that the units forming the coarse bundles consist of a number of fine fibrils. There is a strong suggestion that these tendinous structures normally have a spiral or twisted configuration consistent with the interplay of atrial and ventricular myocardium, which may be described as a "wringing" action. The manner in which the

the reverse applies to the left ventricular wall, where the combined thickness of the two layers by far exceeds that of the right wall. The *interventricular septum* represents the most robust part of the heart. Because the surface on both sides is broken by trabeculation, this structure is characterized by an over-all spongy appearance.

Vague, perimyseal connective tissue planes separate the component fasciculi comprising the myocardium Because of the intricate arrangement of cardiac muscle, it is exceedingly difficult to demonstrate fully discrete connective tissue planes separating individual muscle bundles As already described, the ventricular musculature is organized into *superficial* and *deep spirals*. In general, the interventricular septum forms an integral part of the left ventricular wall upon unrolling the heart muscle.

A meshwork of fleshy trabeculae comprises the trabeculated zones These interanastomosing bundles, the *trabeculae carneae*, are undermined by a labyrinth of sinuous intertrabecular spaces. As a result, the inner surface of the ventricles is broken into irregular muscle folds. In addition, apparently tendinous remnants of hypotrophied muscle trabeculae (aberrant or "false" tendons) can be found among the trabeculae carneae. The *papillary muscle columns* are strongly differentiated muscular trabeculae which serve as stays for the chordae tendineae. Prenatally, the chordae tendineae were derived from well-developed muscular trabeculae, the chordae musculares

The power of intrinsic automatic contraction is a unique property ascribed to cardiac muscle. However, a neurogenic control regulates this myogenic contraction The unit of structure of the myocardium, namely, the *cardiac muscle fiber* or *cell*, is characterized by the fact that it is apparently in syncytial continuity with the remainder of the muscle units of the myocardium. Throughout, transverse striations, similar to those found in skeletal muscle, serially segment the cardiac muscle cell Cardiac muscle differs fundamentally from the former in the arrangement of nuclei and in the smaller caliber of fiber. The cross striations observed are the result of *dark bands*, opaque to light (anisotropic), that alternate with *bands transmitting light* (isotropic) Generally, the nuclei are oval-shaped and are situated along the central axis amidst a homogeneous perinuclear mass of sarcoplasm Myofibrils, or threadlike fibers separated by a sarcoplasmic interstitium, pass uninterruptedly through the full length of the muscle fiber and appear to be interconnected at a platelike condensation called the *Z disk*. The Z disk or membrane occurs at regular intervals, cutting the entire width of the fiber transversely. Tapered accumulations of sarcoplasm, devoid of fibrils, extend from each end of the nucleus, forming a spindle-shaped island of sarcoplasm containing the nucleus. The free surface of the cardiac muscle fiber is provided with an opaque sheath, or *sarcolemma*. The sarcolemmal membrane is not so well differentiated as that found in skeletal muscle.

The cardiac muscle fiber ranges from 12 to 21 μ in diameter. In transverse sections, the delineating sarcolemma is readily seen investing fibers roughly oval to polygonal in shape. In such sections, the cut ends of the myofibrils appear compacted into bundles separated by an interstitial matrix. The irregular configuration of bundles thus mapped is referred to as *Cohnheim's fields* In its simplest form, the cut end of a muscle fiber reveals an even distribution of fibrils. Small opaque bodies called *sarcosomes* are sharply outlined in cross sections while the *nucleus*, when present, lies typically in the center If the plane of section passes through the clear, fiber-deficient zones near the poles of the nucleus, the myofibrils appear to be arrayed peripherally, resulting in a cartwheel effect Patches of glistening textured material may sometimes also be seen in such sections

JUNCTIONAL TISSUES

The primary divisions of the heart are demarcated principally by two fibrous disjunctional zones The paired chambers, viz., the atria and ventricles, are separated at the AV junction. The transitional plane disconnects similar tissues and represents a zone of discontinuity between the musculature of the atrial and ventricular walls. A similar zone, called the *conotruncal junction*, separates the great arterial trunks from their respective ventricles In contrast to the former, fibrous tissue separates histologically dissimilar tissues at the conotruncal level The transition of tissue at this zone involves the replacement of the ventricular musculature by the smooth mus-

dially as a sheet into the septal leaflet of the tricuspid valve. By introducing a light into the left ventricle, the membranous septum can be clearly delineated by transillumination as a vertically oriented elliptic window facing the right ventricle. Employing the same technique in the right ventricle, the septum can be similarly identified from the left as a horizontal oval. The size and configuration of the septum is variable, although its relationship to its associated structures is constant. Smooth muscle may sometimes be contained within the endocardium of the right atrial wall, peripheral to the septum. The structural homologue of the septum membranaceum is represented in the beef heart by an ossified plaque (*os cordis*).

Fibrous Trigones. The trigones are areas of fibrous condensation situated along contiguous areas of the fibrous annuli. Normally, these condensations are the most strongly developed fibrous areas of the cardiac skeleton, which may at these points be modified into fibrocartilage. With advancing age, the trigones may be transformed by progressive calcification into osseous tissue similar to that found in the comparable structures (os cordis) of hearts of lower vertebrates. The base of the aortic leaflet of the mitral valve, which is united by fusion to the aortic annulus, bridges the interval between the two trigones. This leaflet, together with the associated valvula of the aorta (Fig 1-17A), forms a composite valvular apparatus which extends downward from the sinal wall as an uninterrupted membrane to partition the ventricular cavity. The membranous area between the aortic annulus and mitral valvula is fused with the adjacent left atrial wall and serves to reinforce this zone. Upon freeing the atrial wall from this intermediate fibrous lamina, a bare subaortic valvular area (lamina affixa) is exposed. As a result, the annulus fibrosus in this region is ill defined. However, the position of the annulus is indicated by the line of basal attachment of the mitral leaflet, although the right segment of the AV annulus in this locality is less well differentiated than the remainder of the annulus.

THE CARDIAC VALVES

Anatomically, the aortic and pulmonary valves are similar, each being comprised of three semilunar cusps identical in histologic composition and configuration. The following account applies essentially to both valves. In each case, the cusps consist of a central plate of dense fibrous tissue invested in a sleeve of endocardium. The central plate represents the main supportive element and is connected at its valvular base directly to the annulus fibrosus. The annulus and central plate are histologically similar, being composed of coarsely interwoven collagenous bundles, among which may sometimes be found islets of chondroid tissue. The afore-mentioned areas also represent favored sites of calcification.

The arterial (holding) surface of the individual valvulae faces the sinal wall of the corresponding arterial trunk and, in each case, is covered by a relatively thin endocardium containing a minimal amount of subendothelial elastic tissue. In contrast, the endocardium along the ventricular (distensible) surface is thicker and contains a proportionately denser functionally significant elastic lamina. The afore-mentioned stratum may lie directly bound to the central plate or may be separated from it by a loosely arranged band of connective tissue. At a point midway along the free margin of each valvula is located an apical nodule of fibrocartilage called the *nodulus Arantii*. These noduli make possible the more effective closure of the occlusal margins of the semilunar cusps during diastole. The remainder of the adjoining free margin is thinned out into a membranous crescent, called the *lunula*, which consists solely of duplicated endocardial layers.

As previously described, two valves guard the AV ostiums in order to assure unidirectional flow through the cardiac chambers and to prevent regurgitation. Anatomically, the valves differ principally in the number of leaflets they possess. Histologically, the individual leaflets are double-layered, being composed of an atrial fibroelastic lamina and a ventricular tendinous lamina clothed in endocardium. The fibroelastic lamina occupying the atrial surface contains an extensive amount of elastic tissue. This increase in elastic elements permits maximum distention of the leaflet. The deep layer of the fibroelastic lamina is modified into a supportive central plate of dense fibrous tissue, sometimes containing isolated patches of fibrocartilage. The tendinous layer occupying the ventricular surface is identical to the chordae tendineae in tissue composition. The tissue of this basal lamina forms a continuous sheet with the chor-

tendons of insertion of the musculature of the heart wall terminate at the annulus fibrosus has been described previously. The collagenous fibers that make up the tendon of the ventricular myocardium originate from the endomysial planes of the cardiac muscle layers. Some of the afore-mentioned collagenous filaments are received directly into the sarcolemma of the muscle fibers. This mode of attachment is typical and is similar to the origin of chordae tendineae from papillary muscles. In each case, the tendons concerned are the fibrous remnants of cardiac muscle that underwent prenatal atrophy.

When carefully examined, serial sections suggest that muscle fibers of fine caliber arise from the heart wall to enter canalicular interstices which extend for variable distances into the fibrous junction. When a musculotendinous junction of an individual muscle fiber is studied, it can be seen that the collagenous constituents of the tendon are in morphologic continuity with the sarcolemmal and endomysial membranes of the muscle unit Additional delicate fibrils from the tendon can be ascertained spreading centrally into the body of the muscle fiber.

The annulus fibrosus of the AV junction thus represents a tendinous strip encircling the waist of the heart In certain isolated areas, the annulus may be modified into plaques of fibrocartilage. The structural plan of the AV junction is such that, functionally, the annulus has a dual origin, arising, as it does, from the tendons of the atrial and ventricular walls but inserting at the base of the associated valvular leaflet. The arrows in Fig. 1-24B indicate the direction of pull of the muscle groups concerned during contraction. The fatty tissue invariably encountered in the sulcus clearly finds a purpose in consolidating and reinforcing this part of the heart wall.

Chordae Tendineae. In addition to the areas already described, muscle tendon junctions occur typically at the points of implant of the chordae tendineae into the papillary muscles At these transitional zones, the collagenous fibers of the cords enter the papillary muscles to diffuse along the lines of the endomysial planes Moreover, some of the collagenous fibers concerned are matted to the sarcolemma, while additional fibers apparently penetrate deep into the core of the muscle cell. Modified muscle fibers of the terminal conducting (*Purkinje*) type are also found at the bases of the papillary muscles.

Figure 1-25 shows part of the tricuspid valve viewed from its inferior aspect. The leaflets have been freed from the ventricular wall along their bases. Two papillary muscles cut at their roots remain attached to the chordae tendineae; the larger member is part of the anterior papillary muscle. The figure illustrates the manner in which the chordae tendineae fan out in the intervalvular spaces, where they meet the margins of the valvulae. Other chordae tendineae enter the valve leaflets at their apical margins. The primary tendons break into several secondary branchings, some of which extend completely across the inferior surface of the valve. In removing the valve, a cuff of myocardium was retained, attached along its basal border. A number of the afore-mentioned tendons can be seen inserting directly into this ventricular myocardium. In addition, some diminutive papillae can be seen arising from the myocardium of this region. A few, less well-developed tendons take origin from these mural papillae.

Septum Membranaceum. The body of the septum membranaceum consists roughly of an oval-shaped fibrous plaque The septal tissue is composed primarily of densely interwoven bands of collagenous fibers. The fibrous septum is directly continuous with the annular membrane encircling the base of the aorta. According to Fig 1-18, it can readily be seen how the right sinal wall of the aorta bulges outward into the upper margin of the septum. Cardiac fibers of the right atrial wall are similarly connected to the superior border of the septum membranaceum The upper segment of the membranous septum can thus be split into two fibrous laminae, viz., atrial and aortic layers. The inferior margin of the septum overlies the crest of the interventricular septum musculare The two septa are structurally interconnected by dense fibrous tissue Running between these two structures is the cordlike *bundle of His*, composed of modified cardiac muscle Many of the collagenous fibers arising from the inferior circumference of the fibrous septum are tendons of insertion for fibers of the muscular septum. Also originating from the right face of the membranous septum are collagenous bundles that descend subendocar-

encountered suspended within the cytoplasm, the finer granules of which may represent precipitated glycogen

Contractile Elements. Histologically, the cardiac muscle cell presents a textural spectrum resulting from regular segmentation of the fiber in the transverse plane This repeating cardiospectrum is composed of light-transmitting areas which alternate with areas opaque to light. The zones concerned are regarded respectively as isotropic and anisotropic, because of their characteristic reaction to polarized light. In addition, it can be demonstrated by electron microscopy that the isotropic bands permit electron transmission (electron-lucent bands), whereas the anisotropic bands behave negatively to electron passage (electron-dense bands) The structural modification described is in reality due mainly to intracellular filaments, referred to as myofibrils, which apparently course uninterruptedly throughout the entire length of the muscle fiber. The *myofibrils* are generally regarded as the cellular elements of contraction, among which are discernible two principal categories of *filaments*, viz., *thick* and thin filaments The thick *myofilaments* (*A fibrils*) resemble bamboo sticks (Fig. 1-28) as a result of their cylindric form, which is interrupted at regular distances by *varicosities.* The thin fibrils (*B fibrils*) are columns of minute parallel threads (*protofilaments*) organized in sheafs interconnected at some points with neighboring bundles. The intersections of the bamboo-stick fibrils, together with parts of the adjoining B filaments, are aligned vertically at regular intervals to form a continuous membrane called the Z *band* (Fig 1-28). As a result of this "banding effect," it is possible to subdivide the muscle fiber into secondary blocklike units called *sarcomeres* Two successive Z disks form the lateral borders of a single sarcomeric block. Each Z disk is fixed peripherally to the sarcolemmal membrane which completes the perimeter of the individual sarcomeres The disk in question is the most prominent transverse striation of the muscle fiber. The cardiospectrum of the sarcomere can be broken down into an *I band,* defined by the isotropic substance containing the Z membrane, and an *A band,* designating the remaining centrally located *anisotropic* zone. The A band is bisected by a *distinct* electron-lucent *H band,* which is in turn similarly divided by an electron-dense *M strip* Unlike the Z band, the remainder of the cross striations do not bridge the entire interval between the sarcolemmal borders The myofilaments are conceded to be partially in anasto- [illegible]

of the Z bands while the bands of the spectrum become mutually compressed

Intercalated Disks. In addition to the transverse striations, already described, prominent, unevenly spaced plates of condensed anisotropic material cross the muscle fiber. These plates, designated as intercalated disks, are

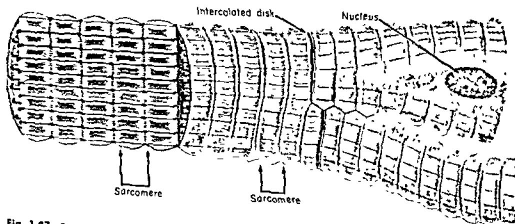


Fig 1-27. Composite schematization of a cardiac muscle fiber.

dae, both consisting of intricately arranged coarse collagenous bundles which are the atrophied tendinous remnants of cardiac muscle that prenatally normally occupies the inferior valvular surface. As a result, the tendon layer is usually not uniformly complete, particularly in the case of the septal and aortic leaflets. Irregular aggregations of fibrocartilaginous nodules (*noduli Albini*) are frequently found along the free margins of the valvulae, which are particularly prominent in the heart of the newborn and are perhaps analogous in function to the comparable structures found in the semilunar valves. The endocardial lining of the ventricular surface of the valve contains a minimal amount of elastic tissue. The AV valves differ from the semilunar valves mainly in the presence of an additional layer, viz., the supportive tendinous lamina. Not uncommonly, nests of attenuated cardiac muscle fibers can be found in the valve leaflets; these are nests of cardiac tissue that normally develop in this location prenatally. In addition, isolated slips of cardiac muscle from the atrial wall may infrequently descend variable distances over the proximal portions of the valves Within the endocardium, patches of smooth muscle fibers are often encountered

CARDIAC MUSCLE[1]

Nucleus. The nucleus of a cardiac muscle cell has a characteristically round or oval form (Fig 1-27). The location of the nucleus is essentially central; its longitudinal axis is oriented parallel to that of the main fiber The nucleoplasm has a spongy texture but is, however, sharply outlined, because of a well-defined limiting nuclear "membrane" The intranuclear material is condensed into a reticulated framework which becomes somewhat altered in appearance during alternate states of rest and contraction of the muscle cell. One or more nucleoli may also be present. Around each pole of the nucleus are visible tapered accumulations of granular sarcoplasm. Two nuclei, usually contiguous, may sometimes occupy the same sarcoplasmic islet.

Sarcoplasm. The muscle cytoplasm (mesoplasm) consists of a homogeneous intracellular matrix within which is contained a profusion of fibrils. In particular the sarcoplasm is concentrated around columns of organelles, the periphery of the muscle fiber, and in spindle form around the nucleus. Coarse ergastoplasmic granules are apparently also contained in the sarcoplasm.

Sarcolemma. A well-defined external limiting membrane, the sarcolemma, invests the muscle fiber. Electron microscopy has revealed the sarcolemma to consist of two distinct membranes, namely, an inner plasma membrane (exoplasm) and an outer fibrous membrane. Histochemically the reaction of the external tunic is similar to that of collagen. At the transition points of muscle tendon junctions, the sarcolemma appears converted into collagen, suggesting that this membrane is primarily a precollagenous material. At these junctions, the tendon fibers grade imperceptibly into the sarcolemma. Fine fibrils fray from the surface of the sarcolemma to commingle with the outlying collagenous elements contained in the endomysium.

Organelles. Columns of diversely shaped intracellular organelles, categorized inclusively as *sarcosomes* (sarcosomata), may be found massed interstitially among the groups of fibrils, as well as embedded within the sarcoplasmic spindle enclosing the nucleus. Most prominent of the organelles, regarded as endoplasmic derivatives, are the filamentous *mitochondria*, which frequently lie aligned in columns parallel to the fibrils The mitochondria are regarded as highly active enzymatically, which may account for their presence in profusion in the cardiac muscle. Electron microscopy has revealed the mitochondrion as an elongated saccular structure apparently circumscribed by a double limiting membrane The internal layer of the membrane is usually folded threadlike into the interior of the organelle. In addition to mitochondria may be distinguished numerous *sarcosomes* having spherical and diskoidal forms The function of this group of bodies is obscure. An ill-defined and controversial Golgi apparatus, located in the vicinity of the nucleus, has also been described. In the aggregated sarcoplasm containing the nucleus may be found cellular inclusions such as droplets of neutral fat and small brownish pigment granules which increase with advancing age. Granules of varying size are also

[1] The ultrastructures described in this text are based principally on the findings of Dr. Bruno Kisch.

digitation, platelike condensations of intracellular material are apparently formed. In other situations, the sarcomeric units of adjacent muscle fibers lie directly in vertical line to produce a crossing-over effect. The intermediary gap contained within the intercalated disk and representing the terminal boundaries of adjacent muscle fibers has an irregular, or festooned, configuration. These sites of apparent intercellular boundaries are first observed in the fetus near term and become increasingly numerous with advancing age.

Capillaries. The heart wall is provided with a rich vasculature. Capillaries run along the endomysial planes paralleling the muscle fibers and periodically form transverse loops which enlace the individual fibers. That the accompanying capillaries bear an intimate relationship to the muscle fibers is borne out by the fact that the endothelial cells of the capillary wall are at many points juxtaposed to the *sarcolemma*, the two being separated merely by an investment of delicate supportive tissue. Indeed, there is some evidence that the capillary may project beyond the sarcolemma to enter the cytoplasmic interior of the muscle fiber.

CONNECTIVE TISSUE ELEMENTS

Collagen is the predominant connective tissue of the heart. A delicate endomysium, rich in fibroblasts, is present within the interstices between muscle fibers. The fibrous tissue comprising the cardiac skeleton is particularly dense and may often show signs of chondrification. Developmentally, the supportive tissue is derived from two separate sources, first, the splanchnic mesoderm (which is a condensed mesodermal layer from which is also derived the myocardium); and secondly, endocardial cushion tissue, a mesenchymal-like concentration of cells that gives rise principally to the valves. The presence of tissue elements of the embryonic type in the postnatal heart is well established. Mesenchymal cells have been described in addition to muscle cells of the undifferentiated type. The cells of an Aschoff body are apparently derived from these embryonic stem cells. The controversial *Anitschkow cell* has been variously described as a primitive proliferative myocyte and also as a fibrocyte. The Anitschkow cell is characterized by a nucleus, cylindric in form, which possesses a barlike mass of chromatin having a serrated border. From the serrated border arise reticulate processes, which in turn are attached to the nuclear membrane. In cross section, the condensed bar of chromatin is located in a clear nuclear field, resulting in the so-called "owl-eye" effect. Well-differentiated histiocytes, sometimes referred to as myocardial reticulocytes, are also found in the interstitial tissues.

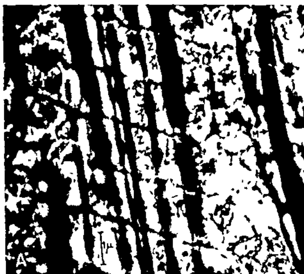
The epicardium is a serous membrane investing the heart wall externally. The mesothelial layer consists of an epithelium which varies from a simple squamous form to cuboidal. The underlying connective tissue is irregularly arranged and concentrated principally in the sulci. The epicardial layers within the sulci follow the territory of distribution of the major coronary vessels and are sites of accumulation of adipose tissue.

The inner lining of the heart, the *endocardium*, is structurally homologous to the intima of blood vessels. Throughout, the endothelial layer consists of an endothelium of simple squamous cells overlying a lamina of connective tissue. The endocardium is thickest in the atria but relatively thin in the ventricular cavities. Patches of smooth muscle are sometimes encountered in the subendothelial layer.

With regard to the individual muscle fiber, an enmeshing net of delicate reticular and elastic fibrils is found intimately matted to the sarcolemmal membrane. This argyrophilic connective tissue acts as a supportive framework in association with the nutritive capillaries and endomysial tissue.

REGULATORY ADNEXA

Developmentally, the postganglionic neurons and cell bodies contained in the cardiac ganglia are derived from the neural crest. In addition, accessory tissue of similar neural crest origin develops in close relation to the heart and great vessels. This adjunct tissue is composed of *chromaffin cells*, so termed because of their histochemical reaction. Condensed clusters of these cells are found widely distributed throughout the body in association with the sympathetic ganglia and are collectively referred to as the "chromaffin system," or *paraganglia*. In regard to the heart, chromaffin cells are strewn generally over the left atrial wall,





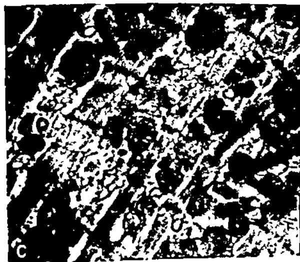




Fig. 1-28 A Cardiac muscle from ventricle of human heart showing myofibrils interconnected at the Z bands. ×4,000 *(From Kisch and Philpott, 1953)* B. Sarcolemma and detailed arrangement of myofibrils ×18,000 *(From Kisch and Bazdet. Electron Microscopy of the Heart 1951.)* C. Guinea pig heart muscle, ventricle Between myofibrils are rows of sarcosomes. ×5,600. *(From B. Kisch, 1956)* D Electron photomicrograph of a longitudinal section through a cardiac muscle fiber from guinea pig. Arrows point to double-membraned intercalated disk. *(From Maximow and Bloom Textbook of Histology. Saunders, 1957 Courtesy of F. Sjostrand.)*

unique to cardiac muscle and occur principally as a structural modification of the Z membrane. Using electron microscopy, investigators have revealed these anisotropic inscriptions as double-layered membranes, advancing the concept that the intercalated disks actually are modified intercellular boundaries. The ultrastructure of the intercalated disk seems to indicate an apparent interruption of the continuity of the muscle fiber, thus opposing the concept of myocardial syncytium The simplest pattern encountered shows the intercalated disk obliterating the Z line across the entire width of the fiber. However, the disk may be indented at some points to produce a staircase effect (*treppe*). In these cases, the disk consists of vertical fractions interconnected by delicate horizontal protoplasmic bridges involving more than one sarcomeric unit Various vertical levels of the individual sarcomeres lying adjacent to the intercalated disk may be displaced horizontally from their expected position. Along the plane of slippage, the sarcomeric blocks lying in parallel rows may interdigitate, often producing a "vernier" effect. At the sites of inter-

This ganglion is designated as the *sinoatrial ganglion* and is directly related to the nerve that penetrates the sinoatrial node. The remainder of the cardiac ganglia are aggregated in close relation to the interatrial septum and in particular enter its basal portion At this point, the cardiac nerves form a depressed area in the cardiac wall called the "fossula nervina cordis," whence arise neural filaments and cell bodies that penetrate the AV node as well as its associated bundle Throughout, ganglion cells are distributed along the course of the coronary vessels and their branches within the sulci

Two principal specialized nerve endings are found in the heart wall, namely, nonencapsulated and encapsulated types. The free, or nonencapsulated, endings have a clover-leaf form and are found within the epicardium. These endings are apparently sensory in function and may also show a gnarled configuration Similar endings have been found in the endocardium. Encapsulated endings containing the forms described are also present in the same tissue layers The fibers, previously described, directly penetrate the muscle fiber sarcoplasm and apparently are the motor units innervating the myocardium. These fibers are by far the most widely dispersed neural elements. It cannot be overemphasized that these neural tissues are richly vascularized and *function as composite* neurovascular organs.

THE CONDUCTION SYSTEM

GENERAL ANATOMY

Sinoatrial Node The sinoatrial node (of Keith and Flack) is a small spindle-shaped mass of specialized heart muscle tissue, usually about 7 mm long and 3 mm wide It was described definitively by A Keith and M W. *Flack (1906)* on the basis of dissections and microscopic study after physiologic investigation had indicated the existence of some such pacemaker in its general area Usually, the SA *node (as it* is commonly called) lies in the groove between the lower end of the *superior* vena cava and the back of the right auricular appendage on the roof of the right atrium This groove is known as the *sulcus terminalis* and corresponds to a crescent-shaped ridge visible on the roof of the right atrium, called the *crista terminalis* *The SA* node is usually not visible grossly without special *dissection* The area where it *generally lies* is often covered with a thick layer of adipose tissue under the epicardium or visceral *pericardium* of the area The SA *node* lies between the epicardium and the myocardium *of the* right atrium and is not visible on inspection of the endocardial surface of the right *atrium In* the human heart, the SA node is often little *different* in gross appearance from the neighboring atrial muscle and the fibrous rings *around* the orifice of the superior vena cava, and it may be densely infiltrated with fat as well Occasionally, it can be distinguished, however, on careful dissection if its characteristics are known These are better brought out on inspection of the SA node of a large mammal, such as the horse or one of the ungulates For example, in the horse's *heart* (Fig. 1-30A), the SA node may be *clearly seen* as a long fusiform structure lying *in the sulcus* terminalis, a little more *on its left than* on its right side, after the *endocardium has* been carefully pulled away. Frequently, several small strands of muscle extend up *over the* neighboring portion of the superior vena cava and may appear to blend with *branches coming* to this area from the deep cardiac plexus, principally the *right vagus and* sympathetic portions From the *inferior, anterior,* and left ends or edges of *the SA node*, long delicate branches may be traced *over the nearby auricular* and atrial muscle, with which they blend after a variable distance *of a few millimeters* to occasionally several centimeters in length These atrial branches of *the SA node* branch in a simple dichotomous form and vary in number from two to about *seven*.

A most conspicuous landmark leading to identification of the SA *node* is the artery to the orifice of the superior vena cava This is a relatively constant *branch of either* coronary artery which comes to the lower end *of the* superior vena cava and the area of the sulcus terminalis In the majority of human hearts, this *vessel* arises from the upper edge of the right coronary *artery* a few millimeters from its orifice in the aorta and passes backward and upward along *the left* side of the right auricular appendage, where it *can* be easily traced ...

but principally along the sulci and in the interval between the aortic and pulmonary trunks. The function of chromaffin cells is obscure.

Carotid Body. A small, irregular condensation of epithelial-like tissue located within the adventitia of the internal carotid artery lies saddle-fashion over the carotid bifurcation above the level of the carotid sinus. This modified cellular mass is referred to as the carotid body (*glomus caroticum*) but is no longer classified as a member of the paraganglia. The constituent cells are pale-staining, with a polygonal epithelioid form, and are arranged in irregular cords resting adjacent to the endothelium of sinusoidal spaces. As a result of its rich vascularity and epithelioid cell composition, this mass resembles an endocrine gland histologically, but it apparently possesses little secretory capacity. In addition, the carotid body is profusely supplied with nerve endings and is assigned the function of chemoreception. Reacting to alterations in blood chemistry (carbon dioxide concentration, oxygen tension, and blood pH), this organ promotes respiratory reflexes in response to conditions of a critical nature. Similar aggregations of tissue are present along the arch of the aorta, the pulmonary trunk, and at the origin of the right subclavian artery at the level of the ansa subclavia.

Aortic Body. The aortic body (*glomus aorticum*) comprises an ill-defined mass, lodged within the subaortic recess at the level of the ligamentum ductus arteriosum. Histologically, the aortic body resembles the carotid body and consists of an irregular condensation of epithelioid cells. Some cells from this mass are strewn along the interval between the aorta and the pulmonary trunk. Fibers of the vagus nerve penetrate the aortic body.

Further cardiovascular regulation is mediated through certain vascular areas described as *pressoreceptive*. Specialized nerve endings, delicately sensitive to alterations of blood pressure, terminate along areas of the heart wall and great vessels. Two particular sites concerned with pressoreception are the carotid sinus and the arch of the aorta.

SPECIALIZED NERVE ENDINGS

The section on cardiac innervation dealt with the origin and distribution of the neural fibers along their extracardiac course. The following is an account of the intracardiac course and terminations of the same nerve fibers together with their associated ganglia.

The terminal fibers of the cardiac nerves enter the heart wall along the lines of reflection of the supporting mesocardial membranes. The resulting nerve plexuses and their associated ganglia may consequently be divided into two major groups. One group passes ventral to the transverse pericardial sinus and is transmitted via the arterial mesocardium, thereby reaching the roots of the great vessels. This nerve plexus is designated as a *bulbar* or *arterial plexus*. A second group courses dorsal to the transverse pericardial sinus to enter the heart wall by way of the venous mesocardia. This latter concentration is related to the dorsal walls of the atria with their entering veins and, as a result, is termed a *venous* or *sinoatrial plexus*.

These plexuses contain intimately related fibers arising from both the parasympathetic and the sympathetic cardiac nerves. The cell bodies of the terminal ganglia enter into synapses with the preganglionic fibers that leave the vagus. In general, the intracardiac fibers are poorly myelinated. Comparatively, the vagal fibers are more uniform and distinctly thicker than the accompanying sympathetic branches. Pericellular and pericapsular terminations have been consistently recognized at the synapses of the preganglionic neurons of the parasympathetic fibers. In contrast, the postganglionic neural fibers are finer and are generally interrupted by varicosites along their neuraxes. Traced to their final distributions, the intimately associated parasympathetic and sympathetic fibers become indistinguishable. At their terminations the threadlike fibers parallel the individual muscle units for some distances and periodically intertwine with the muscle. There is some evidence to suggest that some filaments ultimately pierce the sarcolemma in order to enter the cytoplasmic core of the muscle fiber.

The cardiac ganglia are more abundantly scattered over the left atrial wall than over the right and are particularly profuse along the AV sulcus and in relation to the ostiums of the pulmonary veins. On the right, the cardiac ganglia are arranged along the atrial attachment of the caval mesocardium, a mural zone situated adjacent to the interatrial septum. In this locality, a distinct ganglionic mass lies medial to the orifice of the superior vena cava.

the transmission of a stimulus from the atria to the ventricles. W. His, Sr. (1886) did not seem aware of any muscle bundles passing between the atria and ventricles Kent (1893) described for the first time the bundle of muscle which passes between the lower right side of the interatrial septum into the upper part of the interventricular septum, on the basis of studies on human hearts and those of many mammals These findings were confirmed by W His, Jr (1893). Their discovery has been confirmed by most students of this subject with occasional exceptions In animals an injury by a cut or ligature can be placed so as to change a normal mechanism to complete AV block, as proof of the specific role of the AV bundle The spot to place this injury to the AV bundle is easily located as just anterior, and possibly a little inferior, to the "dimple of the heart" (Roberts, 1958)

Atrionodal Strands. In the lower part of the interatrial septum and posterior wall of the right atrium, several short small strands of specialized conductive cardiac muscle tissue may be found, which blend above with the ordinary cardiac muscle of the atria and, at their lower ends, with the expanded knoblike upper posterior end of the atrioventricular bundle described by Kent and His These atrionodal strands are usually 2 to 10 in number and are threadlike, or less than 1 mm in size. In length, they are usually 1 to 3 mm but occasionally may be traced for longer distances before blending with the ordinary atrial muscle Their role is presumed to be transmission of the impulse from the atrial muscle to the AV node by gathering together the impulse which has spread wavelike over the general wall of the two atria The specificity of these atrionodal strands may not always be apparent, but it seems plausible that they are relatively constant and significant structures. They pass from the atrial muscle into the area of the fibrous skeleton through a fairly dense plexus of connective tissue fibers

Atrioventricular Node (of Tawara). The AV node is a slightly expanded club-shaped area at the upper posterior right end of the AV bundle (Fig 1-31A). It is somewhat flattened from side to side and is highly variable in contour and prominence. It lies with the upper end of the AV bundle in a fairly constant position in a triangle bounded by the orifice of



Fig. 1-30 A Sinoatrial node (of Keith and Flack) with its large atrial branches, in the sulcus terminalis between the orifice of superior vena cava and the right auricular appendage. Horse's heart (*From Roberts, in Sodeman's Pathological Physiology and Mechanisms of Disease. 1950. Courtesy of Saunders*) B Left branch of AV bundle, penetrating "undefended space" of interventricular septum just below cusps of aortic valve. Large branches going toward anterior and posterior papillary muscles form an intricate subendocardial plexus from which intramyocardial fibers penetrate the myocardium Beef heart, injection with india ink (*From Roberts, 1932*)

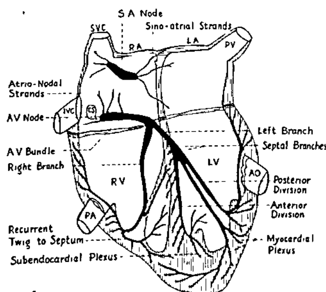
nary artery a few millimeters from its orifice in the aorta, in which case the artery winds around the back of the aortic ring, crossing the roof of the left atrium and the interatrial septum, and reaching the sulcus terminalis Rarely, this portion of the artery to the orifice of the superior vena cava is small, poorly developed, or absent, with its place being taken by a larger vessel reaching the sulcus terminalis from the posterior and right end of the sulcus In such cases, this posterior artery arises from the coronary artery in the posterior coronary or atrioventricular sulcus near the posterior crus at the junction of the interatrial and interventricular septa In about 80 per cent of human hearts, the coronary artery in this area will be the posterior terminal or circumflex part of the right coronary artery whereas in the other cases it may arise from the terminal part of the circumflex branch of the left coronary artery In either case, the artery of the orifice of the superior vena cava gives rise to a branch, *the artery of the SA node*, which passes through the long axis of the SA node, usually entering from its anterior or left end.

Variations in the shape of the SA node are fairly common. It may be shorter and thicker than usual, or it may be elongated and narrower, resembling a nerve Sometimes the SA node is branched and shaped like a Y, with its branched limbs pointing downward over the atria.

On cross section, the SA node usually is triangular or wedge-shaped, with the point of the wedge toward the myocardium, endocardium, and cavity of the right atrium. This contour is more conspicuous in the middle part of the node, which is more often circular near its extremities

Atrial Conduction Pathways. The atrial pathways of the conductive system are the branches of the SA node which pass from the node over the right auricular appendage, down into the upper part of the interatrial septum, and over onto the roof and anterior wall of the left atrium. Usually, after a very short distance of a few millimeters, these atrial pathways blend with the ordinary atrial muscle so as to be indistinguishable therefrom. Occasionally, larger or more conspicuous branches may be traced through the interatrial septum or further into the left part of the left atrium, but usually there is no constant or clear-cut pattern for such atrial conduction pathways. It is a general belief that the impulse is conducted over the atrial chambers through the ordinary cardiac muscle instead of over the specialized pathways which were described in the past (Figs 1-29A and 1-30A)

Atrioventricular Pathways. The AV pathways were described before the SA node, after it became evident from the work of Gaskell (1883) that some pathway was necessary for



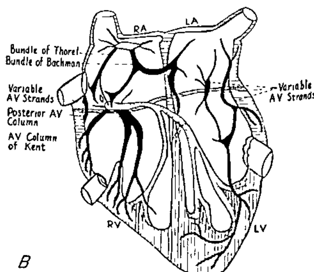


Fig. 1-29. A. Diagram of the constant portions (solid black) of the sinoatrioventricular conduction system of the heart (shaded). B. Diagram of the portions (solid black) of the conduction system which have been described but are generally questioned, shown in relation to the constant structures (stippled).

nection on the atrial side between the bundle and the ordinary heart muscle is, therefore, not very *intimate*. Cohn (1909) concluded that the connection between the atrium and the AV node was constant in mammals of many different kinds, although the junction was subject to considerable variation according to the position occupied by the node and the fibers uniting the atrium and the node. He found that the atrionodal fibers might *join the node* on any surface of it He suspected that anatomic variations at the AV nodal junction should be explained as due to embryologic variations in the formation of the AV groove near the membranous intraventricular septum Moreover, Wenckebach (1906) noted a delay in the passage of the impulse between the atria and ventricles as a confirmatory point on the existence of the AV node and bundle The work of Tawara, Keith and Flack, Fahr, and others on the two

Roberts, 1937–1956, Lev et al, 1949–1957).

Atrioventricular Bundle (of Kent and His) (Fig 1-31A). As described by Kent (1893), His, Jr. (1893), and a great many others since then, the AV bundle is a specific, constant structure which serves the important role of coordinating the contraction of the atria and ventricles.

In the human and canine heart, it is often difficult to identify it by dissection because of its close adherence to surrounding fibrous connective tissue, but in the heart of ungulates and in occasional human hearts, it is readily identified by simple dissection because it is surrounded by a sheath of fibrous connective tissue containing a space filled with lymphlike fluid.

The AV node is found as the expanded upper posterior end of the bundle From the node, the bundle runs anteriorly to the upper part of the interventricular septum, passing slightly to the left and caudally toward the apex as the isolated heart is viewed in the usual position for dissection. The topographic relationships of the AV node and its branches may vary considerably with changes in size or position of the various chambers due to congenital or acquired anomalies The AV bundle is about 10 to 20 mm in length and 1 to 3 mm in diameter. It is slightly flattened from side to side but may be more or less circular in cross section In its central axis may be found a fairly constant artery arising either from the septal branches of the anterior descending branch of the left coronary artery or from the posterior ventricular branches of either the right or left coronary artery.

The relations of the AV bundle and node are of importance in locating the structures and in understanding their pathologic changes in response to disease Covering the surface of the AV node and bundle on its right side are the atrial endocardium in the upper part, and the septal cusps of the tricuspid valve and the endocardium of the right ventricle in its lower part. On the right and posterior surface of the node and bundle in the upper part is the muscle of the interatrial septum, in the lower part, are the fibrous trigone and the annulus fibrosus of the tricuspid valve, as well as the membranous or undefended space. This is the thin, nonmuscular part at the upper edge of the interventricular septum Slightly above and to the left and posterior to the lower end of the AV bundle is the aortic valve ring, usually the commissure between the right coronary and the noncoronary cusps. Further anteriorly and cranially lie the orifice of the pulmonary artery, the right fibrous trigone, and the roof of the right atrium with the first portion of the right coronary artery, and further anteriorly and to the left is the origin of the left coronary artery and its branches The orifice of the coronary sinus is one of the important landmarks for locating the AV node and bundle The coronary sinus itself, as well as the right coronary artery or occasionally the left circumflex coronary artery in the posterior AV groove (in addition to fat, nerve plexuses, and epicardium in the groove), lie posteriorly and to the left of the AV node and upper part of the bundle The cardiac dimple near the orifice of the coronary sinus is a useful guide for a cut or ligature through the AV bundle to produce a complete AV block. Superiorly or cranially is the limbus of the fossa ovale, which occasionally is a foramen ovale or interatrial septal defect.

Surrounding the AV bundle and to a lesser extent the AV node and its atrial nodal branches, is a fibrous sheath known as the *sheath of Curran*. According to Curran and Lhamon (1913), this is a constant bursa, or lubricating mechanism, in relation with the AV bundle. Between the fibrous sheath and the bundle itself is a prominent space or bursa cavity which is conspicuous enough in the hearts of the beef, sheep, deer, and other ungulates so that a needle can be placed in the space for the injection of india ink or other material The fibrous sheath and its space of Curran extend along the main branches of the AV bundle, as well as in a variable degree along the subendocardial and intramyocardial arborization

the coronary sinus, the orifice of the inferior vena cava, and the small septal cusp of the tricuspid or right AV valve. Grossly, the AV node may have the appearance of fibrous tissue, as its specialized muscle components blend with the connective tissue of the area.

Blending with the upper and posterior margins of the node and the upper part of the bundle are a few of the atrionodal strands of conductive tissue described above, as well as a rather abundant plexus of nerve fibers and ganglia, predominantly from the left portion of the deep cardiac plexus, some of them may be detectable on careful dissection. After injection, or occasionally by dissection, *the artery to the AV node and bundle* may be found, coming usually from the posterior atrial branches of the right coronary artery (or occasionally from the left coronary artery, where it supplies the majority of the posterior wall of the heart through its terminal circumflex branch).

The AV node, as described by Tawara (1906a) is a more or less uniform structure which physiologically and clinically is given great importance as a secondary pacemaker in the heart. Van der Stricht and Todd (1919) and Todd (1928), as well as Glomset and Glomset (1940, 1948) have not been able to confirm the usual description of the AV node. On the basis of this failure to identify it, they believed that neither the AV node nor the SA node was identifiable as a structural unit but existed only as a physiologic entity. Although such an opinion may be shared by many casual students of this subject, it seems apparent that each of these units can be identified with appropriate localization of the areas to be studied and the application of proper technical methods.

The AV node according to Braeunig (1904) is separated from the atrial muscle, as is the upper part of the AV bundle, by only two bridging strands of connective tissue, but in the lower portions of the AV node and bundle, more and more connective tissue becomes applied around and through the node so as to surround it entirely in a rather dense sheath. Fahr (1907) described long, thin muscle fibers passing through the fatty tissue of this area surrounding the AV bundle and serving as connections between the AV bundle and the atrial muscle. He indicated that the con-



Fig. 1-31. A. Dissection of atrioventricular node, *AVN*, of Keith and Flack; bundle, *AVB*, of Kent and His; right bundle branch, *RBB*, and left bundle branch, *LBB*. Human, adult heart. Black threads inserted under bundle and right branch. B. Dissection of left branch of atrioventricular bundle, *LBB*, outlined by black threads. Arrow points to an anterior division, cut during dissection. Adult, human heart.

always supplied by branches from the anterior descending branch of the left coronary artery through the septal branches to this area.

LEFT BRANCH The left branch of the AV bundle differs conspicuously from the right. Immediately after the bifurcation, the left branch becomes flattened into a ribbon-like band about 2 to 3 mm in diameter and 0 5 to 1 mm in thickness, and penetrates the interventricular septum through the *undefended space of Peacock* It emerges on the left side of the interventricular septum just below the undefended space, usually located below the commissure between the noncoronary cusp and the right coronary cusp of the aortic valve. When the endocardium is stripped away, and sometimes as viewed through the endocardium, the left branch appears as a *pale, flat, ribbon-like band which spreads out and divides soon into several prominent ribbon-like subdivisions beneath the endocardium on the left side of the interventricular septum* After a variable distance, usually about 20 to 40 mm in the human adult heart, the left branch divides into a *large anterior division* and a *large posterior division* with *several smaller intermediate subdivisions* lying between them The anterior division runs anteriorly and downward toward the apex in the subendocardial tissue, where it branches into numerous smaller unnamed branches which anastomose with each other to form a subendocardial plexus (Fig 1-31A). Most of these strands go to the anterior papillary muscle by running in the trabeculae cordis or columnae carneae in the loose spongy myocardium near the apex In a similar way, the posterior division reaches the region of the posterior papillary muscle.

From the regions of the two papillary muscles of the left ventricle, the subendocardial plexus forms a richly branched and anastomosed arborization plexus on the surface of the two papillary muscles, and from this area branches pass to the subendocardial area on the rest of the anterior, lateral, and posterior walls of the cavity. In this way, a widely dispersed subendocardial plexus is formed, covering the entire cavity of the left ventricle and reaching nearly to the attachment of the mitral valve

In the upper part of the left branch and its subdivisions, *small branches go directly to the upper central portion of the interventricular septum*, thus differing from the usually described arrangement of septal branches from the right ventricle. This may be an anatomic basis for the widely held belief that the stimulus reaches the left side of the interventricular septum shortly before it reaches the right side of the septum.

Subendocardial Plexus (of Purkinje Fibers). The subendocardial plexus already referred to as being formed from the terminal arborizations of the right and left branches, was the first part of the SA conduction system to be described by Purkinje (1839 and 1845). These cardiac fibers were later reviewed and confirmed by Obermeier (1866, 1867) and others, including Paladino (1876), who visualized extensions of atrial muscles into the AV valves as an aid in closure

The subendocardial plexus is usually not strikingly apparent in the heart of mammals other than the ungulates, unless special dissections, injections, or staining methods are used. In some human hearts, the subendocardial plexus may appear as strands which are relatively pale in contrast to the red of the ordinary heart muscle. When revealed by special methods or otherwise, the subendocardial plexus is made up of the larger subdivisions of the two bundle branches and the branching and anastomosing strands which form meshes of variable size Many of the areas between the strands are several millimeters to a centimeter in diameter with a circular or oval contour to the meshes The smaller meshes in the plexus are a millimeter or less in diameter and often are diamond-shaped or rectangular. This plexus is most abundant near the apical part of the anterior and posterior wall and the middle of the interventricular septum of the two ventricles and extending up around the *papillary muscles* According to several authors, the subendocardial plexus is a highly developed and specific structure in the heart of mammals, including man The plexus lies between the endocardium and the myocardium of the ventricle, with a few layers of cardiac muscle overlying it in some areas According to DeWitt (1909), all or nearly all of the trabeculae cordis contain some branches of the subendocardial plexus In many of these strands, which pass freely across the cavity, there are also some bands of ordinary heart muscle. DeWitt made a freehand model of these branches of the AV bundle.

Intramyocardial Plexus. The branches of the subendocardial plexus pass peripherally toward the apex of the two ventricles and radially through the myocardium toward the

plexuses of the conduction system. This makes possible the graphic demonstration of the AV and ventricular portions of the conduction system by the injection of colored material. Curran believed that the bursa was a possible device for spreading infection along the conduction system throughout its entirety when any area of it might be involved by disease, such as rheumatic fever or endocarditis.

Atrioventricular Column of Kent. A bundle of specialized cardiac muscle was described by Kent (1914), which began at the right end of the inferior posterior part of the AV node or bundle and passed through the fibrous skeleton of the heart on the right lateral margin to reach the acute margin of the right ventricle. There it blended with the ordinary cardiac muscle or the subendocardial arborizations of the right branch of the AV bundle of Kent and His. Kent called this the *right lateral atrioventricular junction* or *accessory atrioventricular column.* He described it as a round column of specialized conduction tissue about 3 mm long and 0.5 mm in diameter, closely bound by a connective tissue sheath lying in the middle of the myocardium and a junction of fibrous elements with abundant nerve elements and adipose tissue, in human and other mammalian hearts. This structure has been identified by several authors since then, although many have denied its existence. Wolferth and Wood, as well as Holzmann and Scherf, independently proposed the theory of an *accessory conduction bundle* extending from the atria across the gap caused by the annulus fibrosus and ending in the ventricular myocardium, in order to explain the so-called Wolff-Parkinson-White (W P W) syndrome Rosenbaum et al. (1945) made an extensive study of this condition and surmised the existence of a *"posterior" accessory AV column* running from the AV node into the posterior wall of the right ventricle, as well as the right lateral accessory bundle, as an explanation of the two types (A and B) of the W P.W syndrome.[2]

Other Accessory AV Bundles. Several authors have described other accessory AV bundles which may be found with a fairly high degree of consistency by intensive, precise methods of study. In addition to those just mentioned, Glomset and Glomset (1940, 1948) found numerous strands of muscle tissue bridging the fibrous rings between the atrial and ventricular muscle. Some of them were of ordinary *cardiac muscle type,* whereas others were of the so-called specialized type resembling the Purkinje cells. These are usually very delicate strands and their significance in conducting the cardiac impulse does not seem to be generally accepted.

Ventricular Pathways. At its lower end, where it reaches the undefended space, the AV bundle branches into its two large stems or branches, right and left. This bifurcation rides the upper edge of the interventricular septum, as demonstrated by appropriate dissection with removal of the atria from the ventricle, in a manner resembling the two legs of a man straddling the saddle on a horse.

RIGHT BRANCH. Starting from the bifurcation, the *right branch* runs forward and toward the apex for about 10 to 20 mm. It is a thick, round bundle about 1 to 3 mm in diameter, which is deeply buried in the right part of the muscle of the interventricular septum. When the endocardium behind the septal cusp of the tricuspid valve and the muscle is removed by dissection, the right branch can be clearly exposed in many hearts. Near the junction of the interventricular septum with the anterior wall of the right ventricle, this branch becomes more compact and often passes across the cavity in the so-called *moderator band.* Usually, the moderator band of human hearts is not prominent as in animals, but occasionally it may be conspicuous. More often, in the human heart, the right branch runs through one of the large columnae carneae to reach the anterior wall of the right ventricle near the anterior papillary muscle, the largest of the papillary muscles of the right ventricle. From this point, the right branch divides into numerous strands which form a richly branching and anastomosing subendocardial plexus A fairly constant small branch bends sharply back along the course of the principal right bundle branch to reach the upper part of the interventricular *septum known* as the conus area Other fairly large branches of the termination of the right *branch* leave the area of the anterior papillary muscle and pass along the *inferior* part of the *posterior wall* of the chamber to reach the several *small* posterior papillary muscles, from which numerous branches form the subendocardial plexus of this area.

The right branch of the AV bundle is nearly

[2] See Part 11, Editor.

described by Thorel (1909) but denied by others Rarely, inconstant Purkinje-like fibers may be found in the atrium in the area between the two nodes, but usually they are not so abundant as to form a continuous bridge of specialized tissue between the two nodes Jones (1932) described a connection between the two cardiac nodes in the heart of a human embryo 24 mm long on the basis of serial sections with a wax plate reconstruction He also described a connection between the caudal end of the SA node and the right phrenic nerve but no corresponding connection with the left phrenic nerve. An *interatrial bundle of specialized muscle was described by Bachmann* (1923) in the interatrial septum connecting the right atrium with the wall of the left atrium but was not confirmed by others

The best-known of the inconstant or questionable portions of the conduction system are those strands of specialized or at times ordinary heart muscle tissue which apparently communicate the atria and ventricle at more or less numerous spots around the AV groove These anomalous or congenitally persistent AV strands are much more abundant in the hearts of infants or fetuses than in those of mature adults and probably represent vestigial remains of the more abundant AV connections of the early embryo.

HISTOLOGY

Microscopically, the various parts of the conduction system are made up of varying proportions of three principal types of muscle cells mingled with connective tissue and nerve tissue elements These types will be described briefly with reference to their allocation in the grossly described parts of the system (Fig 1-32).

Purkinje-type Cells. These cells, which are most abundant in the Purkinje fibers of the subendocardial plexus, are commonly thought of as most representative of the specialized conductive system However, it is important to realize that they are not the only muscle elements of the specialized conductive system

The Purkinje-type cells are much larger in diameter than the ordinary heart muscle cells In contrast with the latter, which are ordinarily about 12 to 14 μ in diameter, the Purkinje cells are usually 15 to 30 μ in diameter In the stained section, as in the unstained tissue, they appear pale and watery and at times are highly conspicuous in contrast with the other cells There is a prominent sarcolemma beneath which the myofibrils are gathered in small clumps (*areas of Cohnheim*), which are seen in cross section as a wedge-shaped group of dots close to the sarcolemma. Between these clumps of myofibrils, the sarcolemma is open and pale or unstained with a broad zone of clear cytoplasm between the myofibrils and the centrally placed nucleus (Fig 1-32, IV). The nucleus is usually large, relatively vesicular, and rectangular and frequently is lobulated, or two or more nuclei may be grouped together. This led some earlier authors to attribute an embryologic role to these Purkinje cells with the belief that they gave rise to the formation of new heart muscle cells when needed, a belief not held currently When viewed longitudinally, the Purkinje-type cells again appear pale and poorly stained because of the sparsity or rather wide dispersion of the myofibrillar clumps in proportion to the large amount of relatively clear cytoplasm They "bulge" in a knobby way between the very prominent intercalated disks and also near the site of the nuclei (Fig 1-32, III). The transverse striations are relatively faint in relation even to the pale longitudinal striations The fibers branch and anastomose richly, with long narrow meshes in the syncytium Surrounding the individual fibers, as well as the clumps of fibers making up the various strands of the bundle and its branches, are the connective tissue of the sheath described by Curran and, in some areas, a significant space between the connective tissue sheath and the specialized muscle cells in the ventricle. In sections carrying the Purkinje-type cells, there are usually endocardial or subendocardial connective tissue and, in places, ordinary cardiac muscle on the cavitary side of the plexus, with the layers of the ordinary myocardium on the other side of the bundles

Nodal-type Cells. In the AV node and in the SA node, a predominant type of cell is small and narrow, somewhat resembling ordinary heart muscle fibers but also bearing a similarity to the reticular cells of autonomic nerve ganglia.

The diameter of these small cells is 3 to 10 μ The nuclei are much smaller than in the ordinary or Purkinje-type muscle cells, and they are relatively compact These fibers branch and anastomose much more intricately than the other types, so as to form a very compact syncytium The myofibrils, somewhat like the arrangement in the other cells, are much more prominent because of the scarcity

epicardium. The abundance and intramyocardial pattern of this plexus is poorly understood and has given rise to controversy as to its existence and the details of its structure in relation to the ordinary cardiac muscle fibers. This is only partly because of the variation in methods of study used.

When studied by injection of the *sheath of Curran* in the hearts of ungulates, or by the use of specialized staining methods in other hearts, it is easy to demonstrate some or many branches of the subendocardial plexus of *Purkinje fibers* which extend into the myocardium in several common patterns. Usually, the intramyocardial Purkinje fibers leave the subendocardial plexus at nearly a right angle or a slightly obtuse angle with the subendocardial branches of origin Within the myocardium, the Purkinje fibers or specialized conductive tissue fibers penetrate radially through the myocardium for a variable distance toward the epicardium In doing so, secondary branches turn at right angles to pass in a tangential plane in the interstitial connective tissue layers of the ventricular wall In the myocardium, the specialized conductive tissue cells vary in three common ways easier to establish histologically than by gross dissection. The specialized muscle fibers may be continued (1) directly into ordinary heart muscle fibers, (2) by spreading out into the myocardial syncytium in an indefinite manner, or (3) so as to be applied tangentially to bundles of ordinary cardiac muscle According to Robb and associates (1937–1943), most of the intramyocardial conduction system branches are distributed in a specific way to the different spiral muscle bundles and the different layers of the ventricle, going at a tangent to the endocardium, instead of radially to truncated cylinders of myocardium This arrangement and its electrocardiographic relation to lesions of the coronary arteries as they visualized it are not generally accepted Possibly both patterns may occur

In the interventricular septum, the intramyocardial branches penetrate the septum in several ways. In the upper part, branches from the left stem of the AV bundle enter the left side of the septum and pass downward in the septum and spread out toward the anterior and posterior margin of the septum as well as penetrating toward the endocardium of the right ventricle On the right wall of the interventricular septum, there are usually no branches from the right stem of the AV bundle in the upper part, although occasionally they may be found. Most of the interventricular septum on the right subendocardial area in the conus or upper part of the septum is supplied from a recurring branch of the right limb In the lower part of the septum, the arrangement resembles that of the left side of the septum.

The conductive tissue fibers penetrate all surfaces of the papillary muscles, giving these muscles a more abundant supply than many other areas

Transseptal Plexus. A common concept has been that the subendocardial and intramyocardial plexuses of the right and left ventricle are not connected except through the continuity of the ordinary cardiac muscle tissue Obviously the correct anatomy of such transseptal connections is of great basic value in regard to the normal and abnormal ventricular electrocardiogram, as well as to correlated efficiency in work of the two ventricles Mahaim (1931) described "paraspecific" septal fibers leaving the left stem of the bundle in the pars membranacea and reaching the upper left septum first. Special attention has been given to this problem. Wahlin was especially clear in describing communications between the intramyocardial plexus of specialized conductive tissue arising from the right side of the interventricular septum with loose similar strands arising from the left side of the septum. This fusion between the specialized conductive tissue fibers of the two ventricles was most abundant in the lower half of the interventricular septum. This was confirmed, especially in dissections of the beef heart, by Roberts.

Inconstant or Questionable Conduction Pathways (Fig. 1-29B). When a system varies as much as the conduction system in some of its details, has a complicated embryology, and is studied in many species and ages by various methods, it is to be expected that some structures described as part of the conduction system would not be found by other authors or with other methods Some of these questionable pathways have been found at various times by other writers (in addition to the original writer), whereas some have not been confirmed by most students of the subject In the heart of lower forms of *reptiles*, there is a broad band of specialized heart muscle tissue connecting the incomplete SA ring with the AV ring and called the *ligamentum atrioventriculare of Dogiel* (1907) or *the dorsal ligament of Laurens* (1915–1921) Possibly this structure has its homologue in the *bundle of Thorel.* This is a prominent bundle of specialized muscle connecting the SA node with the AV node,

described by Thorel (1909) but denied by others Rarely, inconstant Purkinje-like fibers may be found in the atrium in the area between the two nodes, but usually they are not so abundant as to form a continuous bridge of specialized tissue between the two nodes. Jones (1932) described a connection between the two cardiac nodes in the heart of a human embryo 24 mm long on the basis of serial sections with a wax plate reconstruction He also described a connection between the caudal end of the SA node and the right phrenic nerve but no corresponding connection with the left phrenic nerve An *interatrial bundle of specialized muscle was described by Bachmann* (1923) in the interatrial septum connecting the right atrium with the wall of the left atrium but was not confirmed by others

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Nodal-type Cells. In the AV node and in the SA node, a predominant type of cell is small and narrow, somewhat resembling ordinary heart muscle fibers but also bearing a similarity to the reticular cells of autonomic nerve ganglia

The diameter of these small cells is 3 to 10 μ The nuclei are much smaller than in the ordinary or Purkinje-type muscle cells, and they are relatively compact These fibers branch and anastomose much more intricately than the other types, so as to form a very compact syncytium The myofibrils, somewhat like the arrangement in the other cells, are much more prominent because of the scarcity

of the cytoplasm, and frequently there is no significant clear zone in the center of the fiber or around the centrally placed small nucleus. In the longitudinal sections, the myofibrils may be quite conspicuous and often appear merged with each other (Fig. 1-32). The transverse striations are often not visible, a reason for the possible confusion with nerve fibers using ordinary staining methods. On the other hand, Yater (1930) illustrated clearly the cross striations in the muscle fibers of the SA node in human hearts with high (1,200 diameters) magnification. He described the presence of much more connective tissue between the interlacing muscle fibers than in the ordinary myocardium or elsewhere.

Intermediate Type of Cells. Mixed with the other two types of specialized cells just described are variable numbers of cells which are intermediate between these two extremes and somewhat resemble ordinary cardiac muscle fibers in size; they differ, however, even from ordinary heart muscle fibers in appearing relatively pale and in having the myofibrils grouped in wedgelike areas next to the sarcolemma with a relatively clear zone of cytoplasm in the center and between the clumps of myofibrils (Fig. 1-32).

Conductive System–Myocardial Junctions. Microscopically, and especially after injection of the sheath of Curran and with use of serial sections, the junctions between the myocardial fibers of ordinary cardiac muscle and the terminal strands of conductive tissue confirm the findings suggested grossly by careful dissection.

In some fibers, there is a gradual transition between the two types of fibers, and in other spots,

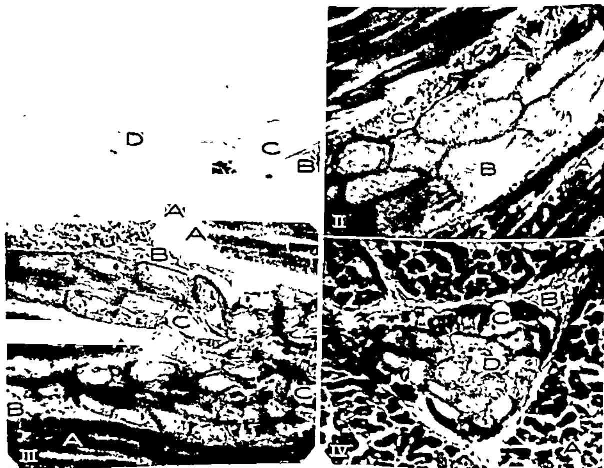


Fig. 1-32. I. Deeply penetrating transseptal Purkinje fiber, D, surrounded by space, C, and sheath, B, of Curran. Sheep heart. II. Striking contrast between merging specialized or Purkinje conducting cells, B, and ordinary myocardium, A, of outer wall of left ventricle in pig's heart. C, sheath of Curran. Note the prominent but sparse myofibrillae present in longitudinally cut Purkinje fiber. ×575. III. Longitudinal section of Purkinje fibers, C, and myocardium, A, of outer left ventricle in sheep heart. B, sheath of Curran; C, capillary. ×337. IV. Sheath of Curran, B, injected with india ink, around Purkinje fibers, D, deep in interventricular septum. Sheep heart. ×337. (From Abramson and Margolin. J. Anat. 1936.)

the transition is abrupt In still other areas, it is impossible to trace any connection between the specialized conductive tissue fibers and the ordinary cardiac muscle cells. Another variation is seen with a tangential application of the specialized muscle fiber on the surface of the ordinary muscle fiber, the continuity between the myofibrils of the two being visible at times

The *cytochemistry* of the conductive tissue has long been of interest but needs more study. Best (1906) described the abundance of glycogen in the heart muscle fibers and prepared a method for staining the glycogen granules with carmine, which is still of great value in identifying the conductive tissue cells. Aschoff (1908) noted the great content of glycogen in the specialized muscle cardiac fibers as contrasted with the ordinary muscle fibers On the basis of their greater abundance in the specialized tissue, the glycogen granules stain a deep mahogany brown when a fresh heart is submerged in Lugol's or other iodine solution According to Del Guerra (1931), the phosphorus and glutathione content of the bundle of His is greater than that of other parts of the heart These and other less-known differences in composition (chemical and histologic) provide use-

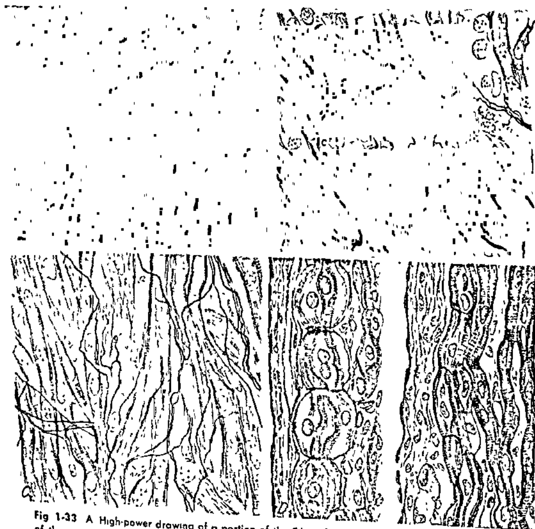


Fig 1-33 A High-power drawing of a portion of the SA *node* Notice paucity and ... of the nerve *fibers* The muscle fibers ... [illegible] ... magnification *Same* as in (A) ... and terminals in the AV bundle near the node, under ... Puppy as in (A) but transition into ordinary myocardial fibers Notice absence of nerve fibers. *Puppy's heart* D (left) Subendocardial Purkinje fibers and (right) their (From Noñidez. Am. Heart J 1943)



Fig. 1-34. A. Rhesus monkey. *A* and *B*, Purkinje fibers of the left bundle branch in longitudinal and transverse section, respectively; *C*, transverse section of ordinary myocardial fibers. Boulin's fluid, Masson trichromic technique. (From Noñidez. Am. Heart J. 1943.) B. Embryologic development of conductive system. The atrioventricular bundle, A.V B., and left branch, on the summit of the interventricular septum at its junction with the dorsal endocardial cushion in a 16 5-mm embryo ×60 A thickening (indicated by the arrow) in the roof of the junction of the right atrium and sinus venosus is probably the early sinoatrial node (SAN) (*Selected from a study of transverse serial sections of human embryos by Walls, in J Anat 1947*) C As in (B) The atrioventricular bundle, A V B., arising from the atrioventricular node and passing into the dorsal endocardial cushion. A slender strand of muscle still connects the left atrium and ventricle, in a 10-mm human embryo The coronary sinus, CS, right venous valve, *R*, of sinus venosus, the interatrial septa, and spongy vascular myocardium (early thebesian or luminal channels) are well shown ×30

ful methods of contrasting the conductive tissue and ordinary heart muscle in numerous staining methods, particularly those for connective tissue or nerve tissue and when the fresh heart is viewed under polarized or ultraviolet light.

The distribution of the several types of specialized heart muscle cells varies in the different portions of the system. The large Purkinje-type cells are most abundant in the branches of the AV bundle and in its lower two-thirds, as well as in the subendocardial and intramyocardial arborizations. In many of these areas, the Purkinje-type cell makes up all of the conductive tissue except for a few elements of the intermediate-type cells which resemble ordinary cardiac muscle somewhat In the AV node and upper portion of the AV bundle, the second type of cells, or nodal type, predominates, forming a tightly meshed reticular arrangement interspersed with only occasional cells of the Purkinje type or intermediate type (Figs 1-32 and 1-33B). A similar arrangement is found in the SA node, where the nodal-type cells predominate in most of the node and its branches In cross section of the SA node, however, all three types of cells may be found in a fairly constant concentric arrangement around the centrally placed artery of the SA node (Fig. 1-32). Next to the adventitia of this artery, there are from one to several layers of the large pale vacuolated Purkinje-type cells which may be very conspicuous and help to identify the SA node in routine sections Outside this zone, there are two other zones composed of the nodal-type cells and the intermediate-type cells in varying proportions, with some intermingling of the two types of cells. Superficial to the SA node is the subepicardial layer of thin connective tissue, and superficial to this tissue is the epicardium of the visceral pericardium. Deep to the node are the ordinary atrial muscle and endocardium of the right atrium. In the hearts of

embryos, young infants, and submammalian species, the specialized or conductive tissue cells are often very small in diameter and have only a few myofibrils, which have poorly stained cross striations These fibers may resemble the embryonic nerve tissue with which they may sometimes be confused on ordinary staining methods, but with specialized staining methods the distinction becomes apparent (Figs 1-33, 1-34).

Neuroanatomy

Grossly, the connections between the nervous system and the conductive tissue may be difficult to identify, but occasionally some strands of the deep cardiac plexus may be dissected On the basis of such dissections, and especially after degeneration of cut nerves, it is generally held that the *right* vagus and sympathetic cardiac nerves end around the SA node and right and left atria predominantly, whereas the vagus and sympathetic nerves from the *left* side end around the AV node with ramifications of variable degree into the ventricles This may be related with the embryologic formation of the heart from the central cardiac tube As it bends and subdivides to form the atria from the part of the tube originally on the right, the ventricular portion is formed from the part of the tube originally developing on the left (Fig 1-35A)

Noñdez (1943), using a silver impregnation technique, described the distribution of the *terminal* nerve fibers in the conduction system as well as elsewhere in the heart Very delicate, *poorly myelinated* or nonmyelinated axons run between the specialized heart muscle fibers upon which they end by basket-like plexuses or, at other times, by nodular end plates. At times, these nerve fibers appear to form a richly anastomosing and branching plexus between the muscle fibers of the SA and AV *nodes*, most conspicuously. In the AV bundle and elsewhere in the *conductive tissue*, the nerve fibers are also abundant and terminate in a similar way upon the muscle cells but form a less densely anastomosing plexus Throughout the conductive tissue, but much more frequently in the neighborhood of the SA and AV nodes, there are large numbers of nerve cells, probably of visceral efferent postganglionic type Even within the *intramyocardial* plexus of the conductive system there are numerous nerve fibers and endings This accounts for the *difficulty* in eliminating entirely the neurogenic theory *of impulse* formation and conduction, although it is usually considered today that these nerve fibers have principally a regulating function rather than a role in the formation of the cardiac impulse

Blood Supply

The blood supply of the conduction system is probably of great significance in connection with the formation of the heart beat and its conduction over the chambers. This has been emphasized by Géraudel (1932), as well as by earlier writers, with confirmation in regard to the SA node by Burch (1957), Roberts (1950, 1956), and others. The *blood supply of the SA node and its branches* is highly constant, a conspicuous artery coming to the sulcus terminalis from the first part of the right coronary artery or occasionally from the left coronary trunk or the posterior coronary artery. There are no constant or significant veins, and the structure is drained by small venules into the cavity of the atrium The *artery to the AV node and bundle* arises from the posterior septal arteries coming from the right or left coronary artery in the posterior coronary sulcus The arteries to the *right branch* of the AV bundle usually come from the earlier septal branches of the anterior descending coronary artery. The *left branch* and the subendocardial, as well as the intramyocardial, plexus are supplied by the branches of the two coronary arteries supplying the various portions of the ventricle.

The *arteriolar supply* of the conductive tissue is similar to that of the ordinary cardiac muscle, and the patterns of the capillaries and venules in the two portions of the heart also are similar. However, vascularity was thought to be much less in the conductive system than in the ordinary heart muscle In the AV and SA nodes, the capillaries may be closer together than elsewhere because of the small size of the average fibers there

The *thebesian* or *luminal vessels* communicating with the endocardial pockets in the right and left ventricles are thought by the author (1943) to be more numerous in the areas overlying the subendocardial arborizations and the right and left branches of the AV bundle While this is difficult to confirm, it seems plausible in the light of a similar embryologic origin of the specialized conductive tissue and the thebesian or luminal system of blood vessels, both of which are vestigial remains of more predominant systems existing *in early* embryonic life.

The lymphatic supply of the conduction



Fig. 1-34. A. Rhesus monkey. *A* and *B*, Purkinje fibers of the left bundle branch in longitudinal and transverse section, respectively; C, transverse section of ordinary myocardial fibers. Boulin's fluid; Masson trichromic technique. (From Noñidez. Am. Heart J. 1943.) B Embryologic development of conductive system. The atrioventricular bundle, A.V.B., and left branch, on the summit of the interventricular septum at its junction with the dorsal endocardial cushion in a 16.5-mm embryo ×60. A thickening (indicated by the arrow) in the roof of the junction of the right atrium and sinus venosus is probably the early sinoatrial node (SAN). (Selected from a study of transverse serial sections of human embryos by Walls, in J. Anat. 1947.) C. As in (B). The atrioventricular bundle, A.V.B., arising from the atrioventricular node and passing into the dorsal endocardial cushion. A slender strand of muscle still connects the left atrium and ventricle, in a 10-mm human embryo. The coronary sinus, CS, right venous valve, R, of sinus venosus, the interatrial septa, and spongy vascular myocardium (early thebesian or luminal channels) are well shown ×30

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6

Arteries, veins, and lymphatic vessels of the heart

JOSEPH THOMAS ROBERTS

The *coronary* arteries and veins, so named because they make a ring or crown about the middle of the heart, have been known for many centuries It is only within the past few decades, however, that great emphasis has been given to certain details of the structure of the vessels nourishing and draining the heart in relationship to diseases of the heart This emphasis reflects the rising rate of illness due to disease of the coronary arteries and recognition that details in the structure and function of the blood vessels of the heart are closely related to possible disturbed mechanisms both in certain forms of heart disease and in the involvement of the heart by extracardiac disease. Many problems remain unsolved as to these details, especially in regard to methods of improving the tolerance of a heart with congenital or acquired lesions.

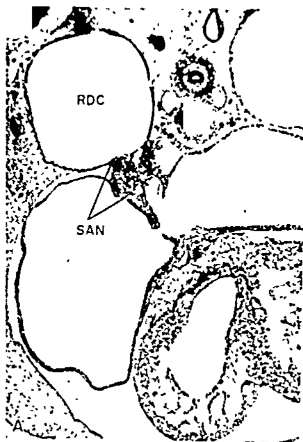
Nourishment of the heart muscle, valves, coverings, and nerve supply comes from oxygenated blood carried through the coronary arte- [illegible]

…of its oxygen content, is drained through numerous tributaries to the large and small coronary veins by which it returns to the general circulation. Some of the plasma reaches a network of lymphatic capillaries somewhat paralleling the blood vascular capillaries Some red cells may reach the lymphatic vessels after local injury, and from this lymphatic capillary bed, this material reaches larger lymphatic collectors near the base of the heart before going to the lymph nodes in the mediastinum, and eventually to the thoracic duct for return to the general circulation

GROSS OR GENERAL ANATOMY

The Coronary or Cardiac Arteries. OSTIUMS OR OPENINGS OF THE CORONARY ARTERIES The orifices, or openings, of the coronary arteries are ordinarily the apertures in the wall of the aorta through which blood passes into the coronary arteries (except for relatively minor amounts reaching the heart through other channels) These orifices, or *coronary ostiums*, are funnel-shaped depressions, somewhat rounded in contour, and ordinarily are found near the center of the sinuses of Valsalva, which are guarded by the right anterior and left anterior leaflets of the aortic valve In the majority of hearts, there is one orifice for the right coronary artery in the right anterior sinus of Valsalva and one orifice for the left coronary artery in the left anterior sinus of Valsalva It is not unusual, however, to have two or more openings for either of these main arteries (Fig 1-36).

The shape of the coronary ostiums is usually a slightly flattened oval or circle but may appear as a narrowed slit The diameter of the orifice is usually about 0 7 to 1 5 mm but may vary between 3 mm and a size barely large enough to admit a pinpoint In the normal young heart, the wall of the ostium, where the coronary artery perforates the aorta, is perpendicular to the wall





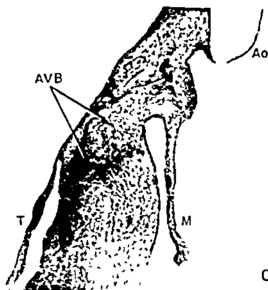


Fig. 1-35. A. As in Fig 1-34B. The compact cluster of cells in the base of the right sinus valve represents the future sinoatrial node, *SAN*. Here, as in the adult heart, it lies outside the right atrial myocardium, probably because of the infolding of the sinus venosus as it is absorbed into the atrium. *RDC*, right duct of Cuvier. The light area between the atrial and ventricular muscular chambers is the fibrous skeleton, with a dark compact mass of cells (at the arrow) representing the upper dorsal part of AV node The spongy myocardium is clearly shown Age 10-mm human embryo ×30 B. The finer structure of the right limb of the AV bundle, composed of compact cells, in a 40-mm human embryo heart. ×650 C Heart of 105-mm embryo with the interventricular and interatrial septa shown in vertical section *AVB*, atrioventricular bundle, with relations to the tricuspid, *T*, mitral, *M*, and aortic, *AO*, valves similar to those found in an adult ×50.

system has received very little attention except for the reference to the sheath of Curran as a "lymphatic space" by Robb et al (1937) The lymphatic nature of the sheath of Curran was doubted by Roberts (1937). There are, however, lymphatic vessels between the muscle fibers in the subendocardial arborizations of the conductive system resembling the subendocardial lymphatic plexus which drains peripherally through the myocardial plexus to the subepicardial plexus of the cardiac lymphatic system Evidence against the sheath of Curran being a true lymphatic channel or lubricating bursa is also seen in the absence of living cells, endothelial or mesothelial, even in sections where they are well stained in capillaries

of the pulmonary artery and its sinuses of Valsalva, and in front of and under the right auricular appendage. It lies superior to the fibrous trigone, as well as the septal and anterior cusp of the tricuspid valve. This artery continues in the AV groove toward the right until it reaches the acute margin of the heart. Then it turns posteriorly and caudally, passing under the arch of the inferior vena cava as it continues its course in the AV sulcus on the posterior surface of the heart.

From this point on, variations occur from one specimen to another according to a reciprocal arrangement with the terminal circumflex branch of



Fig 1-37. Relations of right coronary artery. Photographs of a human heart with anomalous origin of right coronary artery as three separate vessels, 1, 2, 3, from the three ostiums, A, B, C. A. View of the right coronary sinus of Valsalva, with A, small ostium near anterior commissure, and B and C, two small ostiums opening from a single depression near the other commissure. B. View of aorta, Ao, amputated above three right coronary ostiums, A, B, C, leading into three arteries: 1, small artery to base of pulmonary artery, PA; 2, small artery to conus region, 3, main right coronary artery with large branch, 4, the "artery to the orifice of the superior vena cava and sinoatrial node," and its branch; 5, to right atrium, RAA. RV, right ventricle.

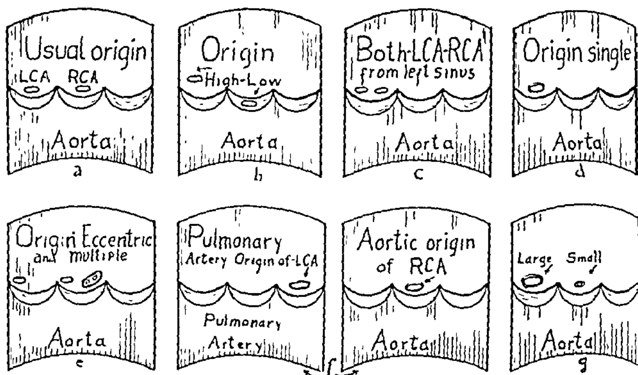


Fig. 1-36. Some variations in origin of coronary arteries from aortic sinuses. LCA (left coronary artery), RCA (right coronary artery) a The typical arrangement with a single orifice for each main artery in the middle of the sinuses of Valsalva. b. Variations in location of coronary ostiums in relation to commissures and lunula, or edge of cusps c. A variation in location and number of ostiums of coronary arteries and their communications with branches. d. A single coronary artery ostium. e. Origin of right coronary artery from three small ostiums, two in a single depression, and an eccentric left ostium. f. Origin of left coronary artery from pulmonary artery (usually anginal or fatal early). g. Variations in size of ostiums from large to very small.

of the aorta. In hearts which are older, rotated, or enlarged in some chamber, the coronary ostium often passes through the aortic wall at a sharp angle This may cause insufficiency of coronary blood flow and may create difficult problems at operation or catheterization

When the orifice is multiple, the two or more openings empty into the early branches of the coronary artery. For example, if the left coronary artery orifice is multiple, there may be two orifices, each of about half the size of the ordinary one Each ostium opens into either the anterior descending coronary artery or the left circumflex coronary artery. Another arrangement is to have two or more smaller openings in the sinus of Valsalva which fuse into a larger channel in the first part of either main coronary stem.

The location of the coronary ostiums is typically shown in the center of the sinuses of Valsalva at the point of their greatest concavity, presumably this is the ideal situation (Fig 1-36). However, it is common to encounter displacement of the ostiums in either direction towards the adjacent commissures between the aortic valves. The level of the ostiums in relation to the *lunula*, or free edge of the aortic cusp, is also highly variable. The ostiums may be on the same level as the lunula of the commissures between the aortic cusps, or one or more millimeters above or below this level. With normal functioning of the aortic cusps, these variations probably have no significance If the aortic valve is diseased or deformed with insufficiency, stenosis, or perforation, hemodynamic variations may acquire considerable importance in the effectiveness with which aortic blood reaches the ostiums of the coronary arteries when they are more than usually displaced from the sinus of Valsalva.

MAIN CORONARY TRUNKS. From each coronary ostium, a vessel emerges which is usually of the "middle-sized artery system" of anatomists. This is a *muscular artery* which carries the blood under high pressure and velocity to its branches for distribution to the muscle of the heart

The *right main coronary artery* (Fig. 1-37) leaves the ostium and runs from the aorta toward the right and anteriorly behind the base

the left coronary artery for supplying the posterior surface of the heart According to Gross (1921), the right circumflex artery terminates near the acute margin of the heart in 4 per cent of hearts, near the crux in 10 per cent, between the crux or posterior interventricular sulcus and the obtuse margin of the heart in 66 per cent, and near the obtuse margin of the heart in the remaining 20 per cent. This agrees with the finding of Barnes (Figs. 1-38, 1-47) that in 74 per cent of hearts, most of the posterior ventricular surface is supplied by the right coronary artery If the right coronary artery reaches the posterior interventricular sulcus, it then turns toward the apex and the left and goes down toward the apex for a variable distance before anastomosing with terminal branches of the anterior descending branch of the left main coronary artery and other vessels around the apex In the 20 per cent of hearts where the right coronary artery supplies the entire posterior ventricular surface, a branch continues in the interventricular sulcus beyond the crux, or junction, with the posterior interventricular sulcus before bending toward the apex and left, or obtuse, margin of the heart.

The branches of the right coronary artery are intermediate in size and often not specifically named After branches to the wall of the aorta (such as the vasa vasorum), there are one, two, or three *anterior ventricular branches*, usually one *lateral branch*, one *right posterior ventricular branch*, and one to three (or even five) *left posterior ventricular branches*, in addition to the larger *posterior descending branch* occurring in 92 per cent of cases. From the right coronary artery, *atrial branches* pass over the front, side, and back of the right atrium and, to a variable degree, over the back of the left atrium, with practically always one or two *anterior atrial branches* and one *lateral atrial branch*, in addition to one or two *right posterior and left posterior atrial branches*. From these branches of the right coronary artery, specific *arteries to the SA and AV nodes* are usually described, as well as branches to the AV bundle of His and its right branch.

The *left main coronary artery* is a sturdy short vessel running from the left coronary ostium in the left anterior sinus of Valsalva, through the aortic wall, and then anteriorly and to the left in the anterior AV sulcus It extends to its bifurcation, which is usually between 1 mm and 1 cm from the wall of the aorta. There, it bifurcates into its two main branches: (1) the *anterior descending coronary artery*, and (2) the *left circumflex coronary artery* These two vessels are so large and are of such importance that they are frequently grouped with the right main coronary artery trunk as the three main coronary arteries.

The left main coronary artery has important relationships. At its origin, as stated, are the lumen and wall of the ascending aorta In front of it, and arching over its upper or cranial surface, are the arch of the main pulmonary artery, the reflection of the superior posterior part of the pericardium, and the oblique sinus of the pericardium. Posterior to the trunk and bifurcation is the anterior wall of the left atrium as it leads into the left auricular appendage The latter lies to the left and is superior to the vessel. Inferior to the trunk are the left fibrous trigone and the anteromedial part of the mitral ring with its anterior leaflet Crossing from in front to above, and then behind the trunk, is the delicate *main terminal channel of the superficial lymphatic system* as it passes to a lymph node leading toward the mediastinum The trunk is surrounded by loose areolar connective tissue and abundant fat of the subepicardium and, toward its bifurcation, by a reflection of the visceral pericardium or epicardium A large vein often lies superior and anterior to the trunk, as the vein passes toward the origin of the coronary sinus

The two main branches of the left coronary artery usually arise at the end of the trunk but

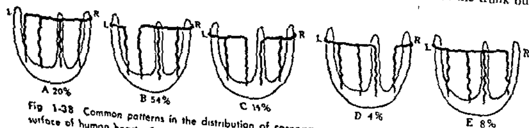


Fig 1-38 Common patterns in the distribution of coronary arteries (right and left) on posterior surface of human heart. (From Barnes, according to Campbell)

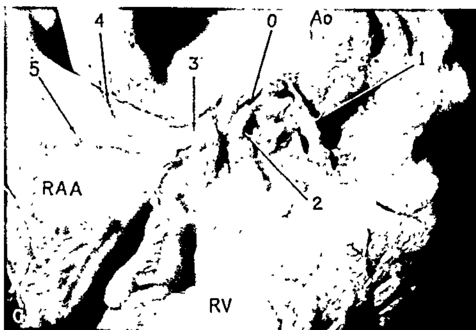


Fig. 1-37 (Cont.). C View, labeled as in (B), from outside of aorta, with small opening, O, in middle artery, 2; *RV*, telae adiposae of right ventricle D View, labeled as above, of right coronary artery, 3, in anterior atrioventricular sulcus, crossed by a prominent anterior accessory cardiac vein, *ACV*, entering the right atrium 6, Anterior right ventricular arteries; *SAN*, sinoatrial node area in sulcus terminalis between right auricular appendage, *RAA*, and superior vena cava, *SVC*.

the root of the aorta and *pulmonary artery*, with their attached valvular cusps and the pericardial reflections.

The *ventricular branches* of the anterior descending artery are several, they pass from an acutely angled origin to the right and across the anterior surface of the infundibular part of the right ventricle, and lower down over its anterior wall. Arising at a similar angle are several other vessels, approximating 1 mm in external diameter, which run to the left and apically over the anterior surface of the left ventricle, these anastomose with each other from above and below, and also with the end twigs of the descending branches of the left circumflex coronary artery, especially with the *obtuse marginal branches* A rather conspicuous whorl of vessels is seen in the vortex at the apex of the heart, arising chiefly from the anterior descending artery, with lesser proportions from the other main arteries In 38 per cent of hearts, the terminal branch of this artery is at the apex, while in 52 per cent of hearts it is in the lower third of the posterior interventricular sulcus and, occasionally, higher on the posterior ventricular surface In a few hearts, the anterior descending artery ends near the middle of the anterior interventricular surface.

The inconstancy in course and character of the coronary arteries is much more conspicuous for the atrial than for the ventricular branches, whether they arise from either the right or the left coronary artery The *atrial branches* of the left coronary artery arise chiefly from the left circumflex artery. Usually, there are one, two, or three *anterior atrial branches*, one *lateral atrial branch*, and one *posterior left atrial branch*

L. Gross emphasized that the left coronary artery (in his series) supplied no branches to the poster [illegible]
tw [illegible]
Th [illegible]
from either the right or left coronary artery, according to which artery predominates in supplying the two atria According to L. Gross, this vessel arose from the right coronary artery in 60 per cent of cases and from the left in 40 per cent of the cases.

PENETRATING OR PERFORATING CORONARY ARTERIES. These channels are most important and are quite variable in number, location, and pattern of secondary branching In general, they arise from the deep or buried wall of the main coronary trunks, their main branches, or their intermediate and unnamed superficial branches Some of the *penetrating arteries* pass directly into the myocardium at an angle which may be acute, perpendicular, or obtuse, as well as tortuous in some cases M. B. Whitten (1930) believed that the perforating branches from the vessels supplying the right ventricle penetrated at a more acute angle to the surface of the heart than those penetrating into the myocardium of the left ventricle, and felt that this accounted for less bending of those in the right ventricle, thereby protecting them from injury leading to atherosclerosis Other authors have been less impressed with this variation (Gross and Kugel, 1933, Spalteholz, 1924; Crainicianu, 1922; Cossio, 1935; Bosco, 1935).

INTRAMYOCARDIAL PLEXUS OF CORONARY ARTERIES. Within the myocardium, the perforating or penetrating coronary arteries fulfill their most important functional role of bringing arterial or oxygenated blood to a richly branching and anastomosing *intramyocardial plexus of arterioles, capillaries, and veins* which penetrate all parts of the myocardium in the four chambers in such a way as to form a network of capillaries around each muscle fiber. There is great variation, however, in the pattern of the larger intramyocardial arteries, there is also considerable disagreement about possibly important relationships of such vessels to the bundles or subdivisions of the ventricular muscle According to earlier workers, and as emphasized by L Gross, the penetrating branches in general pass through the myocardium until approaching the endocardium (Fig. 1-39A). From these penetrating branches, horizontal branches pass in the connective tissue septa or planes between the several layers or subdivisions of the ventricular musculature Between these tiers of horizontal intramyocardial arteries, there are some anastomoses

Several patterns of the penetrating arteries and their subdivisions are common, such as (1) dichotomous branches, (2) larger vessels which penetrate directly to the endocardium or through some less deep portion of the myocardium before terminating in treelike branches, (3) trunks which penetrate a shorter or longer distance before branching at a right angle into comb-shaped smaller vessels Other less identifiable patterns are common On the basis of injections combined with

occasionally arise separately from the sinus of Valsalva.

The *anterior descending coronary artery* is possibly the most conspicuous blood vessel of the heart and has been given most attention by pathologists. It runs in the anterior interventricular sulcus from its origin toward the apex of the heart, which it most commonly crosses for a few centimeters before completing its anastomosis with posterior vessels at the anterior edge of the interventricular septum, made up by the fusing anterior walls of the right and left ventricles. Thus this artery descends in front of the point of origin of the superficial bulbospiral muscle and in the lower, or apical, two-thirds of its course, it descends in front of the superficial sinospiral muscle. Behind or deep to these are the deep sinospiral and deep bulbospiral muscles. Superficial or anterior to the artery (in addition to the left auricular appendage and the visceral and parietal pericardium) are three fairly constant structures. (1) a large coronary vein which is the right one of the pair that accompanies the artery in the sulcus and unites to form the great cardiac vein before it becomes the origin of the coronary sinus, (2) several lateral anastomosing channels of the superficial lymphatic trunk of the anterior ventricular area, and (3) several strands of cardiac muscle and a variable amount of adipose tissue. Still further anteriorly lie the anterior mediastinum with its adipose tissue and the sternum and costal cartilages of the fifth to eighth ribs, the internal mammary artery and vein, as well as intercostal muscles, nerves, and vessels, subcutaneous tissue, and skin.

The *left circumflex coronary artery* is a large artery averaging 2 to 4 mm in external diameter but varying in its size according to a reciprocal arrangement with the other arteries. From its origin, it passes under cover of the left auricular appendage forward and then curves toward the left in the anterior left part of the AV sulcus, in front of and above the fibrous ring and anterior leaflet of the mitral valve. In the first 3 to 5 cm of its course, it is hidden in a thick layer of adipose tissue and frequently a few strands of cardiac muscle. Running parallel to it and superficial or anterior to it is the *great cardiac vein*, as it unites with the large atrial vein to form the origin of the coronary sinus. This vein lies at first inferior or apical to the artery, then anterior or superficial to it, and then cranial or superior to the artery. The latter leaves its close attachment to the coronary sinus as it approaches the obtuse, or left, margin of the heart, where it lies on the inferior or apical floor of the sinus. The artery ends usually between the obtuse margin of the heart and the crux or posterior interventricular sulcus but occasionally may continue into the sulcus as the *posterior descending coronary artery* or, rarely, on to the posterior wall of the right ventricle in hearts were the right coronary artery is less developed.

Branches of the left circumflex coronary artery arise at a rather obtuse angle with this trunk and descend almost parallel to it toward the apex but crossing somewhat more toward the left in general direction. In the great majority of hearts (23 and 45 per cent), there are two or three *obtuse marginal branches*, but sometimes as many as four, five, or six such branches descend from the artery over the rounded or obtuse margin of the left ventricle toward the apex, where they join in the whorl of anastomoses near the vortex by anastomosing with terminal branches of the left anterior descending artery and the right coronary artery.

In 84 per cent of hearts, instead of one *posterior descending branch* of the left circumflex, there may be one, two, or three such vessels. In 8 per cent there is a large *posterior descending coronary artery*, somewhat approximating the left anterior descending coronary artery in size and importance; this vessel, when present, runs from its origin downward and toward the right across the upper part of the posterior surface of the left ventricle, making an acute angle with the main trunk of the coronary sinus. Then, it turns toward the apex and runs in the posterior interventricular sulcus to anastomose with the terminal part of the left anterior descending and other arteries. In 7 per cent of hearts, a small terminal branch of the left circumflex coronary artery, the *right posterior branch*, runs downward and to the right across the posterior surface of the right ventricle and may reach the acute margin of that chamber, where it anastomoses with the acute marginal branches and anterior descending branches of the right coronary artery.

INTERMEDIATE OR UNNAMED SUPERFICIAL CORONARY ARTERIES. The intermediate and unnamed branches of the left coronary artery are *atrial* and *ventricular*, as well as *branches to*

the root of the aorta and *pulmonary artery*, with their attached valvular cusps and the pericardial reflections.

The *ventricular branches* of the anterior descending artery are several, they pass from an acutely angled origin to the right and across the anterior surface of the infundibular part of the right ventricle, and lower down over its anterior wall Arising at a similar angle are several other vessels, approximating 1 mm in external diameter, which run to the left and apically over the anterior surface of the left ventricle, these anastomose with each other from above and below, and also with the end twigs of the descending branches of the left circumflex coronary artery, especially with the *obtuse marginal branches*. A rather conspicuous whorl of vessels is seen in the vortex at the apex of the heart, arising chiefly from the anterior descending artery, with lesser proportions from the other main arteries In 38 per cent of hearts, the terminal branch of this artery is at the apex, while in 52 per cent of hearts it is in the lower third of the posterior interventricular sulcus and, occasionally, higher on the posterior ventricular surface. In a few hearts, the anterior descending artery ends near the middle of the anterior interventricular surface.

The inconstancy in course and character of the coronary arteries is much more conspicuous for the atrial than for the ventricular branches, whether they arise from either the right or the left coronary artery The *atrial branches* of the left coronary artery arise chiefly from the left circumflex artery Usually, there are one, two, or three *anterior atrial branches*, one *lateral atrial branch*, and one *posterior left atrial branch*

L. Gross emphasized that the left coronary artery (in his series) supplied no branches to the posterior surface of the right atrium except *terminal* twigs from the anterior and lateral atrial branches The *superior vena cava ostial artery* may arise from either the *right or left* coronary artery, according to which artery predominates in supplying the two atria According to L Gross, this vessel arose from the right coronary artery in 60 per cent of cases and from the left in 40 per cent of the cases

PENETRATING OR PERFORATING CORONARY ARTERIES These channels are most important and are quite variable in number, location, and pattern of secondary branching In general, they arise from the deep or buried wall of the main coronary trunks, their main branches, or their intermediate and unnamed superficial branches Some of the *penetrating arteries* pass directly into the myocardium at an angle which may be acute, perpendicular, or obtuse, as well as tortuous in some cases. M. B. Whitten (1930) believed that the perforating branches from the vessels supplying the right ventricle penetrated at a more acute angle to the surface of the heart than those penetrating into the myocardium of the left ventricle, and felt that this accounted for less bending of those in the right ventricle, thereby protecting them from injury leading to atherosclerosis. Other authors have been less impressed with this variation (Gross and Kugel, 1933, Spaletholz, 1924, Craimicianu, 1922, Cossio, 1935, Bosco, 1935).

INTRAMYOCARDIAL PLEXUS OF CORONARY ARTERIES Within the myocardium, the perforating or penetrating coronary arteries fulfill their most important functional role of bringing arterial or oxygenated blood to a richly branching and anastomosing *intramyocardial plexus of arterioles, capillaries, and veins* which penetrate all parts of the myocardium in the four chambers in such a way as to form a network of capillaries around each muscle fiber. There is great variation, however, in the pattern of the larger intramyocardial arteries, there is also considerable disagreement about possibly important relationships of such vessels to the bundles or subdivisions of the ventricular muscle According to earlier workers, and as emphasized by L Gross, the penetrating branches in general pass through the myocardium until approaching the endocardium (Fig 1-39A). From these penetrating branches, horizontal branches pass in the connective *tissue septa* or planes between the several layers or subdivisions of the ventricular musculature Between these *tiers* of horizontal intramyocardial arteries, there are some anastomoses

Several patterns of the penetrating arteries and their subdivisions are common, such as (1) dichotomous branches, (2) larger vessels which penetrate directly to the endocardium or through some less deep portion of the *myocardium* before terminating in treelike branches, (3) trunks which penetrate a shorter or longer distance before branching at a right angle into comb-shaped smaller vessels Other less identifiable patterns are common On the basis of injections combined with

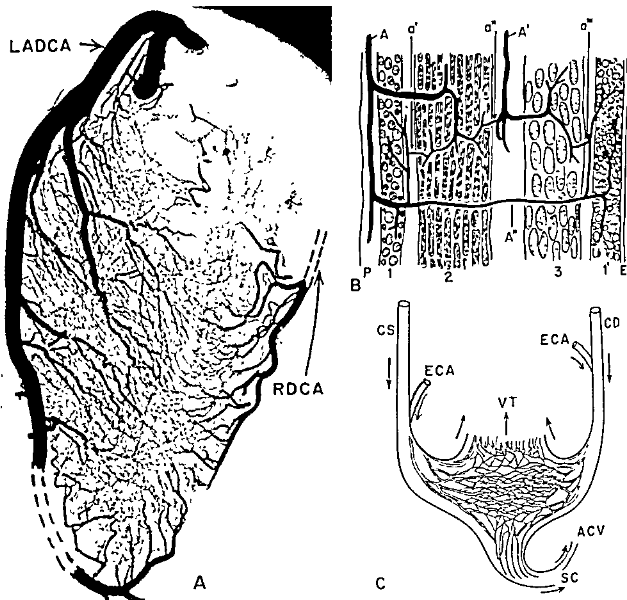


Fig. 1-39. A Patterns typical of the branching of the penetrating or perforating coronary arteries, in the human interventricular septum, with rich anastomosis between branches of left anterior descending artery, *LADCA*, and posterior descending branch of right coronary artery, *RDCA* (*From Crainicianu,* 1922, with added segments as dotted lines. X-ray after injection.) B Diagram illustrating the distribution of arteries among muscle layers of the myocardium *P*, epicardium; *E*, endocardium; 1, 2, 3, 1', myocardial bundles, *A*, subepicardial branch, *A'*, muscular branch; *A"*, branch extending through thickness of wall, *a'*, *a"*, and *a'"*, anastomotic channels (Lowe) C. Diagram of coronary vessels showing the network of capillaries and other channels which receive blood from the coronary arteries, *CD*, right, and *CS*, left, and the extracoronary arteries, *ECA*, and which drain through the coronary sinus, *SC*, the accessory coronary veins, *ACV*, and the thebesian or cardioluminal channels, *VT* (*Modified from scheme of Crainicianu,* 1922.)

unrolling of the ventricular bundles of muscle, Robb and Robb gave great importance to *long intramyocardial arteries* which parallel the surface of the muscle bundles, with restriction of their subdivisions so as to supply only the layer of muscle to which they were attached In this interpretation, these penetrating or intramyocardial arteries were end arteries supplying sections of one of the four important ventricular muscles, so that occlusion (clinical or experimental) was followed by scar tissue in the plane of the muscle bundle involved, instead of causing truncated cones of infarct in the wall Most other workers have given little or no cognizance to such an arrangement of specific blood supply for individual sections of the ventricular muscle bands. It is probable that both patterns exist in various degrees

Endocardial coronary arteries. The endocardium, especially in the thicker left ventricle and in the papillary muscles of both ventricles, is supplied in several ways from either the

superficial coronary arteries or the cavity through the so-called *luminal channels*

Arising from the superficial ventricular arteries, *the endocardial arteries* are terminal small twigs from larger penetrating vessels which have penetrated only a third or more of the distance from the epicardium to the endocardium; in some cases, they are horizontal plexuses of vessels in the endocardium arising from larger penetrating arteries that pass from the epicardial layer to near the endocardium before breaking up into the terminal plexus. This, as well as the role of the luminal vessels, may account for the variations with which myocardial infarction involves or spares the endocardial portion of the thick compact left ventricular wall. The walls of the normal atria and right ventricle are thin and relatively spongy so that the endocardial layers are not so distinct from the superficial layers as in the left ventricle.

ARTERIOLUMINAL CHANNELS AND SINUSOIDS. Vieussens (1706) demonstrated openings of small size in the endocardium of both ventricles and more commonly in the lining of the atria. When he injected carmine and glue into the coronary arteries, he saw plugs of the material protruding from these openings, which he visualized as accessory channels for nourishing the heart muscle. Since then, opinion has differed as to the existence and significance of these channels. Many writers have obtained evidence supporting the existence of these channels connecting the coronary arteries and the lumen of the cardiac chambers. On the other hand, others have failed through inspection, or injection and dissection, to demonstrate such vessels; it has been claimed that the techniques used by Vieussens and others were not adequate, and this seems probable.

Inspection of the endocardial lining of the cardiac chambers, even when unaided by magnification or injection, discloses many openings. They vary in size from that of a pinpoint, or even smaller, to (in a few cases) almost 1 mm in diameter. Some resemble the deeper and larger depressions which are simply intertrabecular spaces. Many of the luminal vessels open in the intertrabecular spaces, a persistence of the embryonic state.

The significance of such openings and their connections cannot be determined by inspection alone. This requires (1) injection either of their orifices or through the coronary arteries or veins, (2) the more time-consuming methods of inspection of plastic casts after corrosion of injected specimens or of wax-plate reconstruction and serial sectioning; or (3) indirect methods of experimental physiology and analytic pathology. It seems clearly proved that there are vessels of arterial structure (as shown in the histologic sections from which wax-plate reconstructions have been made) with communication between the lumen of the heart and the penetrating or intramyocardial branches of the coronary arteries in each of the four chambers (Fig. 1-39C).

Wearn et al. (1933) described three types of such connections according to their characteristics of wall structure and lumen. Some of these arterioluminal channels were arterioles or vessels with relatively thick walls and lumens 10 to 30 μ in diameter. In other areas or sections, the vessel was less clearly arterial, with less muscle in the wall, but was arterial in function, as shown by tracing back through the reconstruction to an origin from a coronary artery. A third variation was found in channels with very thin walls and lumens of variable size and shape, some of which resembled ordinary capillaries and others of which became expanded into large channels with irregular contour and diameters of 30 to 250 μ. The latter were called *sinusoids* because they resembled the sinusoids described in other organs. Some of each of these types of channels end directly in the pores or openings of the endocardium, whereas others go through intermediate phases of capillary networks and venular structure. Some of them communicate directly or in intermediate ways with the *venoluminal channels* which connect the lumen of the chambers with the fine terminal tributaries of the coronary veins. Vessels of this group are of the type originally described by Thebesius (1708); with the heart held immersed in water, he injected air into the coronary sinus and saw air bubbles issue from the "pores" on the endocardium.

Many workers have referred to all these channels communicating with the lumen under the [illegible] capillaries, and sinusoids which connect with the small luminal openings in the endocardium without using appropriate injections or serial sections, it is preferable to refer to these channels as *openings of the luminal vessels* or as *thebesian*

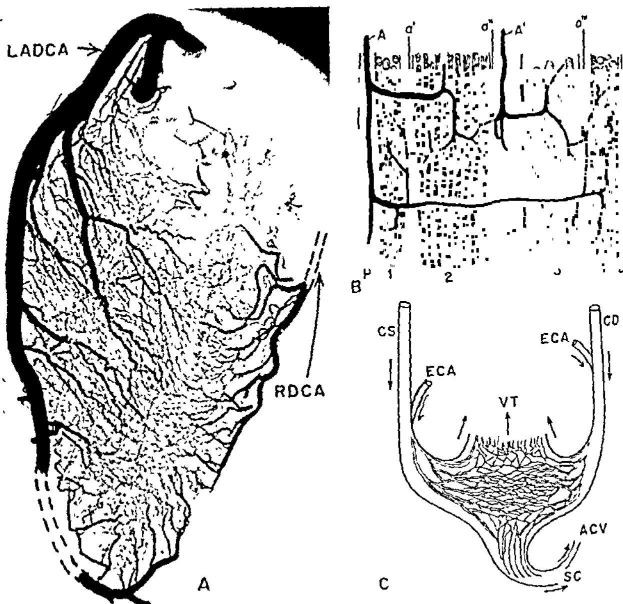


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ENDOCARDIAL CORONARY ARTERIES. The endocardium, especially in the thicker left ventricle and in the papillary muscles of both ventricles, is supplied in several ways from either the

the inner part of the heart wall during early phases of embryologic development. These vascular and muscular components in the spongy part of the heart wall undergo proportionately massive regression as the growth of the coronary vessels and the compact myocardium become predominant in the early formative period of embryologic development

The disagreement between authors concerning the existence, structure, and role of the thebesian or arteriovenoluminal channels is based upon the widely different and often inadequate techniques used and has led to various claims that these channels were (1) of no significance, (2) capable of draining blood from the myocardium into the cardiac chambers, (3) able to carry blood from the chambers of the heart into the myocardium of its walls, or (4) normally insignificant in these roles but capable of assuming significance with gradual narrowing of the principal coronary vessels. *In a series of studies by Roberts and coworkers* (1939–1945), it was shown that when hemodynamic conditions were *controlled, it was possible* for the thebesian channels to either *drain or* nourish the myocardium according to the gradient of pressure between the right or left ventricular cavity and the

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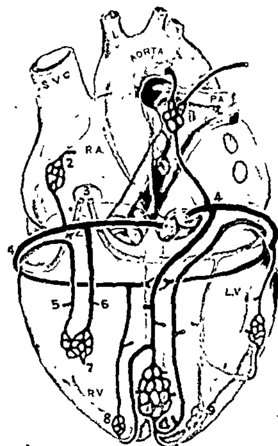
THE INTERCORONARY AND EXTRACORONARY ANASTOMOSES. Anastomoses or communications between the several parts of the coronary system are theoretically of great importance The existence, magnitude, and significance of each of these anastomoses has caused much controversy because of use of various technical methods, often inadequate, by various writers, and perpetuation of dogmatic opinions by authorities who give little evidence of having used skillfully enough the available methods for studying such vessels The concept that each coronary artery and each of its branches was an "end artery" *in the* sense used by Cohnheim and others has been based upon failure of thick viscid injected materials to pass from one vessel into others under the pressure used; infarction and death of animals after experimental ligation of coronary artery branches, and *incomplete* inspection of the connections between vessels in *gross* specimens and injected hearts These anastomoses (natural or induced) might shift blood from an ischemic to a nonischemic area or vice versa Unfortunately, occlusive disease or spasm often involves both these anastomoses and their sources, as well as the artery to an infarcted area, with decrease in expected protection

It now seems established beyond question (Gross, 1921, Schlesinger, 1938, 1940; Prinzmetal, 1947, and many others) that the *intercoronary anastomoses* are fairly abundant between adjacent branches of the coronary *arteries* at all levels of branching. Careful dissection of the terminal branches of the coronary arteries, especially near the apex, often reveals intercoronary anastomoses which are visible to the unaided eye without injection. After injection of colored, coagulable, or radiopaque material, numerous anastomoses between the coronary arteries are visible on inspection, dissection, differential corrosion, and radiography of *specimens (Figs* 1-41, 1-42, and 1-43A). These anastomoses are usually of capillary or arteriolar size, except for the occasional ones of small-arterial or larger size

These channels are demonstrated by injection of watery solutions whereby material injected into one coronary artery quickly appears in other coronary arteries The techniques available do not establish the probable size of such communications *either* during life or in death There still is controversy about the size and extent of these intercoronary artery communications in the normal heart of either man or animals, such as the dog If the injected material, such as barium sulfate or lead agar, is too thick to penetrate the capillaries, these com*munications* are of at least arteriolar size According to Blumgart et al. (1940), only 15 *per cent* of *normal* human hearts were found to have interarterial communications of 30 to 80 μ in diameter. Prinzmetal and others (1947) injected graduated glass spheres and radioactive red cells into the coronary arteries of normal human hearts and concluded that the *largest intercoronary arterial communications* range from 70 to 180 μ (approximately the diameter of arterioles). They also found *that* the thebesian vessels ranged from 70 to 220 μ in *diameter*, and that there are direct *arteriovenous anastomoses* of 70 to 170 μ in diameter, with no *significant* difference between those of the *two ventricles It* should *not* be assumed that these studies are entirely *acceptable* for indicating the size of the anastomoses during life, when the factors of intramural tension and gradients at both *ends* of the anastomoses are of great importance *in affecting* their size Although these anastomoses *are narrow* in proportion to the size

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The number and distribution of the orifices of the luminal channels described by numerous authors differ according to the techniques and definitions used (Grant and Viko, 1929). Generally, it is stated that these orifices are more numerous in the *right* than in the left atrium, more frequent in the *right* than in the left ventricle, and more abundant in the two atria than in either ventricle. The larger openings which are easily seen in the atria must be distinguished from the openings of the *accessory anterior ventricular coronary veins.* Combining injections and inspection of the endocardium with a dissecting scope, the author found the orifices of the accessory channels in the two ventricles to be more numerous in the part of the endocardium covering the right and left branches of the AV bundle (of Kent and His). *This is consistent with the belief that both the thebesian vessels and the conductive system are vestigial residuals of the vascular channels of sinusoidal nature and the loose spongy musculature found on*



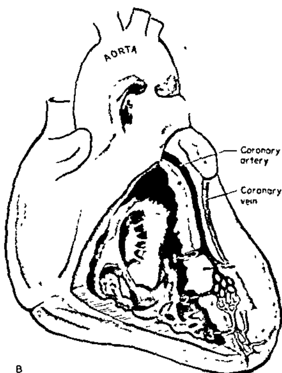


Fig 1-40. Types of anastomoses in the blood vessels of the heart A. Collateral circulation supplying blood to the heart 1, Extracardiac anastomoses between the coronary arteries and other branches of the aorta; 2, accessory coronary veins opening directly into the right atrium; 3, coronary veins ending in the coronary sinus above the tricuspid valve; 4, the left main coronary artery with intercoronary arterial anastomoses to the right coronary artery and between their branches; 5, venoluminal channel (thebesian vein), 6, arterioluminal anastomoses; 7, sinusoidocapillary luminal anastomosis; 8, interarterial anastomosis through capillaries; 9, intervenous anastomoses B Collateral luminal and anastomosis of the right ventricle. 1, Arterioluminal vessels; 2, capillary luminal anastomosis, 3, venoluminal anastomosis. *(From Roberts, in Sodeman's Pathological Physiology and Mechanisms of Disease. Saunders, 1950 and 1956)*

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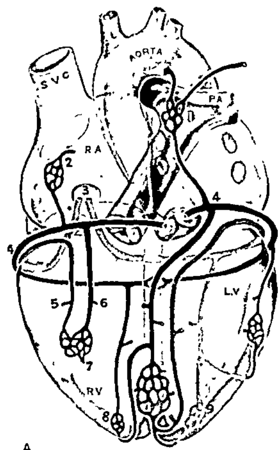
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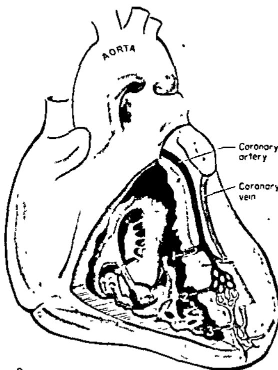


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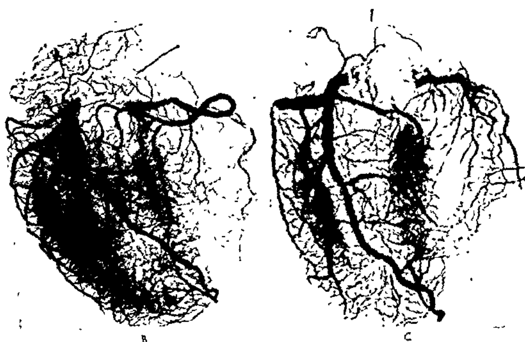


Fig 1-42. *Roentgenograms* after opaque injection of coronary arteries *of human* hearts Each heart is *placed so that* the view is from the back Note the *variability in the atrial* arteries. A. At birth, with *right ventricular* preponderance of relative *size and* vascularity B In an "average" adult *heart* of about 60 years, with left *ventricular vascular* preponderance, and "right coronary artery *predominance*" of posterior blood *supply*. C. In a common variation with "left coronary artery predominance" of posterior *blood supply* from left circumflex artery (From *Gross*, 1921.)

of the main coronary arteries, they are numerous enough so that collectively they represent a sizable communication between the coronary vessels. This undoubtedly is adequate to protect against some degree of cardiac ischemia under certain circumstances, as shown by survival with complete closure of some arteries in either human or animal hearts.

Changes with age occur in the magnitude of the intercoronary anastomoses, especially during growth from infancy to maturity. In the heart of a *newborn child*, the blood supply of the right ventricle predominates, but *by maturity*, a shift has become apparent, with a much more predominant blood supply in the left ventricle. During this development, the interarterial anastomoses between the branches of the right and left coronary arteries, which are minimal at first, become progressively more numerous. *With aging* from early adult life to old age, in hearts considered otherwise normal, there is also increase in the number of demonstrable interarterial anastomoses (Gross, 1921; Schlesinger, 1940). These important conclusions must be evaluated with caution, however, because of the difficulty in excluding either congenital or acquired narrowness of one of the coronary vessels or branches as a stimulus to the development of the interarterial anastomoses.

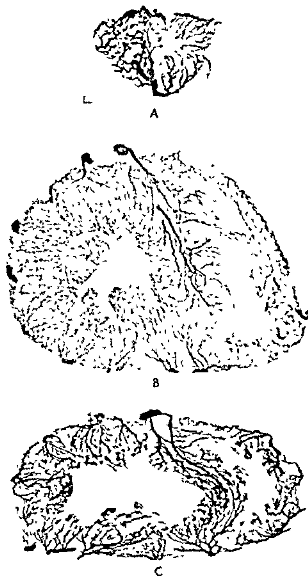


Fig. 1-41. Vascularity, in transverse sections, of the two ventricles at different ages. A. At infancy (11 days), with right ventricular blood supply predominant B. At middle age (32 years), with predominance of left ventricular arteries, especially in the finer penetrating vessels. C. At old age (60 years), with predominance of left ventricular coarse vessels (Photographs of roentgenograms after injection of coronary arteries with opaque material) (According to Gross. The Blood Supply of the Heart. Hoeber, 1921.)

The *extracoronary anastomoses* have generally been ignored in dissections and clinical management of patients, but recently attention has been given them as possible sources for supplementary coronary artery blood flow, either natural or induced (Fig. 1-43B). Since von Haller (1803) first mentioned them, little has been written about *the anastomoses between branches of the coronary arteries and branches of the aorta outside the heart.* In a classic study by Hudson et al (1932), the existence of extracardiac anastomoses and their possible contribution to coronary blood flow was placed on a firm basis. By injection into the coronary arteries, the branches of the coronary arteries around the ostiums of the pulmonary veins, pulmonary artery, the superior and inferior venae cavae, the root of the aorta, and the pericardial reflections about the large vessels were clearly demonstrated and found to anastomose with branches of the internal mammary arteries and other branches of the aorta. Through these anastomoses, injection of the coronary arteries under controlled conditions allowed the injected material to flow into the vasa vasorum of the thoracic aorta and pulmonary artery, as well as into vessels of the parietal pericardium, diaphragm, pleural surfaces of the lungs, bronchi, mediastinum, trachea, and esophagus, as well as occasionally into vessels of the skin over the neck and over the jaw. Supplementing this study, Mortiz (1932) reported extensive anastomoses be-



Fig 1-42. Roentgenograms after opaque injection of coronary arteries of human hearts. Each heart is placed so that the view is from the back. Note the variability in the atrial arteries. A At birth, with right ventricular preponderance of relative size and vascularity. B. In an "average" adult heart of about 60 years, with left ventricular vascular preponderance, and "right coronary artery predominance" of posterior blood supply. C. In a common variation with "left coronary artery predominance" of posterior blood supply from left circumflex artery. (From Gross, 1921.)

tween branches of the coronary arteries (especially in the tela adiposa, or fat pads, around the coronary arteries) and the vessels supplying the parietal pericardium in four hearts where the pericardial cavity was obliterated by chronic adhesions.

On the basis of the two studies, Moritz et al. suggested to Beck and Tichey (1935) and to Mautz and Beck (1937) that pericardial adhesions would be useful in revascularizing hearts with coronary artery occlusion Since then, they and many others have conducted extensive experiments on animals and patients It is claimed that patients with coronary insufficiency can be benefited by the production of pericardial inflammation However, present evidence does not support these claims in the opinion of some writers For example, the author has often seen cut pericardial adhesions bleed more freely from the cardiac end Doubt that pericardial adhesions are more likely to bring new blood to the coronary arteries than to drain it away led Roberts (1938–1958) and others to initiate other more direct methods to revascularize the heart. Some of these include (1) arteriolizing the coronary sinus or veins by anastomosis of an artery to the sinus, implanting an artery in the sinus; implanting the open sinus into the left ventricle, or making a fistula from the ventricle to the sinus; (2) connecting coronary arteries to other arteries; (3) puncturing the endocardium of the left ventricle or carrying opened vessels across the cavity of the ventricle; and (4) implanting a skeletal muscle, lung edge, artery, auricular appendage, or other structures into the ventricle wall or cavity.

Although it is clear that the intercoronary and the extracardiac anastomoses are present in various degrees in all hearts, their value in protecting against coronary disease of severe progressive nature is inadequate Their potential significance, however, is indicated by the finding of hearts with extensively narrowed coronary arteries which have survived with considerable activity and cardiac reserve For example, several hearts have been described (Wearn, 1927, and others) in which the ostiums of both coronary arteries have been completely occluded for a long time by chronic fibrotic disease (syphilis usually), and it is common to observe hearts with a high percentage of the lumen of both coronary arteries being chronically obliterated by atherosclerotic plaques. In such cases, it is surmised that the role of the intercoronary anastomoses, the thebesian vessels, and the extracardiac anastomoses must have been very active during life There are no adequate studies of these specimens to support this hypothesis with evidence about the direction and magnitude of blood flow through the accessory pathways

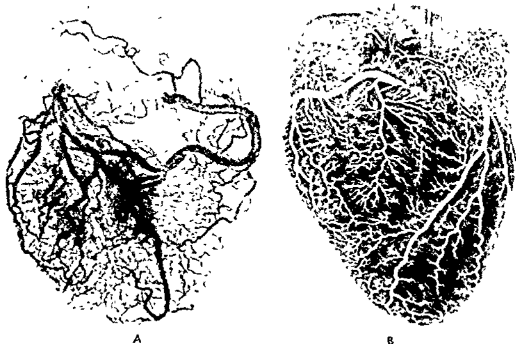


Fig. 1-43. A. Posterior view of an "average" heart of the eighth decade, with balance between right and left coronary arteries B. Anterior surface of an injected and cleared heart of the fourth decade, showing the distribution of the arteriae telae adiposae and vasa vasorum of the pulmonary artery, with interarterial anastomoses.

Similarly, the possibility of a reflux, or ebb and flow, through the coronary sinus (or other coronary veins) suggested by Batson and Bellet (1930) remains a possibility which may occur in experimental laboratories but which has not been proved as a significant mechanism during the normal life of human beings. Observing a patient with drainage of pulmonary vessels into coronary sinus plus seeing revived human hearts beat as well with perfusion through the sinus as via the coronary arteries led Roberts (1938–1945) to develop his method of arterializing the coronary sinus. This method, developed at his request by Beck, Bailey, and others, despite its technical difficulties, still seems the most effective way to revascularize a heart.

BLOOD SUPPLY OF THE ATRIA, PULMONARY ARTERIES, AORTA, HEART VALVES, AND PERICARDIUM. As indicated above, branches from adjacent coronary arteries supply each of these portions of the heart, with anastomoses as described for the ventricular arterial supply. The *right atrium* is supplied anteriorly and laterally by the branches of the right coronary artery, and usually by the posterior atrial branches from the right coronary artery. Occasionally, if the left coronary artery supplies predominantly the posterior wall of the ventricles, the right posterior atrial arteries may arise from the circumflex branch of the left coronary artery. An important branch is the *ramus ostii venae cavae superioris*, which arises from the first part of the right coronary artery and passes over the roof of the right auricular appendage to end around the mouth of the superior vena cava. In so doing, it supplies a rather conspicuous branch to the area of the sulcus or groove between the superior cava and the right auricular appendage in which lies the SA node. Rarely does this vessel arise from the left coronary artery.

The *left atrium* and *auricular appendage* are nourished by anterior, lateral, and posterior atrial branches, usually from the circumflex branch of the left coronary artery. Occasionally, the left posterior atrial arteries arise from the end of the right coronary artery.

The *interatrial septum* is supplied by penetrating b[illegible]

[illegible] supply, at times, posteriorly from the end of the left circumflex artery.

The adventitia of the pulmonary artery and *aorta* is abundantly supplied by small branches from both the right and left coronary arteries, which arise as these arteries pass through the wall of the aorta as vasa vasorum, and from the first few branches of the coronary artery supplying the fat pads and pericardial reflections around these vessels. These branches of the coronary arteries anastomose quite freely in the wall of the first part of these great vessels with other vasa vasorum which arise from extracardiac branches of the aorta and from the lumen of the aorta or *pulmonary artery*.

Blood vessels are often seen in the AV and semilunar heart valves (Fig. 1-41). These valvular vessels are most abundant in hearts with persisting *extensions of atrial cardiac muscle* into the base of the AV valves or muscle strands in the base of the semilunar valves (Dow and Harper, 1932). For this reason, such valvular vessels are most often seen in the hearts of infants, children, or young adults, where muscular extensions have not atrophied as in older hearts.

Opposing views as to the presence of these vessels in "normal" hearts have been inevitable with the different criteria for defining a normal state. Most authors have used the presence of blood vessels in adult hearts as a basis for the diagnosis of chronic inflammation (Gross and Kugel, 1933). On the contrary, Wearn et al (1936) described rather abundant blood vessels in the valves of adult human hearts in which there was no history or other microscopic evidence to support a diagnosis of previous inflammation. They, therefore, concluded that blood vessels exist in normal heart valves of adults and that these vessels could be demonstrated regularly with use of proper techniques for injections.

The blood supply of the *pericardium* is from (1) branches along the two phrenic nerves from the subclavian or upper part of the internal mammary artery, (2) parasternal branches from the lower internal mammary arteries and intercostal arteries, (3) phrenic branches from the superior epigastric and posterior mediastinal arteries. They form a sparse plexus of threadlike, small vessels chiefly along the phrenic nerves and the pericardial contacts with the diaphragm and sternum. Anastomoses occur with (1) the branches of the coronary arteries in the pericardium around the great vessels, (2) the subdiaphragmatic vessels, and (3) other branches of the aorta to the chest wall

and thymus area. Hypothetically, these may be of help in revascularizing an ischemic heart.

BLOOD SUPPLY OF THE CONDUCTING SYSTEM. The SA node in man is usually supplied by a large branch which enters the node and runs through its center while giving lateral branches which anastomose with vessels in the adjacent atrial muscle. This *artery of the SA node* is a branch of the artery of the ostium of the superior vena cava. In turn, this artery is nearly always a branch of the right coronary artery which arises near its ostium as one of the first anterior atrial arteries This vessel ascends over the front of the right auricular appendage to reach the sulcus between the ostium of the superior vena cava and the base of the appendage on the roof and posterior wall of the right atrium. This pattern is present in more than 70 per cent of hearts, and in 25 per cent of the cases, the principal stem of the artery of the ostium of the superior cava arises from the end of the left coronary artery as a branch of the circumflex branch of the left coronary artery when it forms the posterior descending artery. In some of the other hearts, the artery of the SA node arises from both coronary arteries. In rare cases, there is no distinct vessel to be identified.

The AV node lying near the mouth of the coronary sinus is supplied by a *posterior atrial artery* supplying the posterior wall and portion of the atrial septum. This artery arises in about 92 per cent of hearts from the posterior portion of the right coronary artery. This vessel enters the AV node and continues into the axis of the AV bundle, while giving anastomosing branches

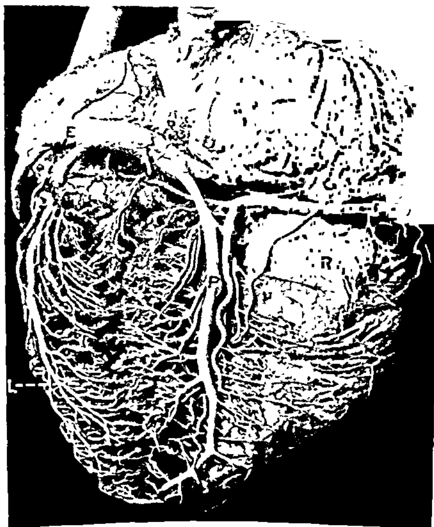


Fig. 1-44. Posterior view of celluloid cast of heart from a child, aged 14 years. The left ventricle is markedly more vascular than the right. *R* indicates the right ventricle; *L*, the left ventricle, *P*, the posterior interventricular vein; *E*, the left coronary artery, *F*, the right coronary artery (*From Whitten*, 1930)

to the node, bundle, and first portions of the two stems The right stem of the AV bundle usually receives most of its blood supply from *perforating septal branches* of the anterior descending branch of the left coronary artery as they penetrate the interventricular septum Occasionally, when the right coronary artery supplies a predominant portion of the interventricular septum, the *right stem* receives its blood supply therefrom also The *left stem* is supplied by interventricular septal branches from both the right and left coronary arteries, chiefly from the anterior descending branch of the left coronary artery and some small vessels from the posterior descending artery, which usually is a terminal branch of the right coronary artery. The *subendocardial arborization network of Purkinje* in the intramyocardial plexus of conductive tissue receives its blood supply from the various branches of the two coronary arteries supplying the myocardium of the area, as described elsewhere, and varying in different hearts

Cardiac Capillaries and Sinusoids. The capillaries of the heart are its most essential vessel, as they nourish the contracting muscle cells and the other tissue elements of the organ The purpose of all the other vascular arrangements in the heart is to make possible the role of the cardiac capillaries They are tiny tubes with a simple endothelial wall and vary in diameter between 3 and 12 μ. The capillaries begin as small branches of the terminal *arterioles* which penetrate the fibrous sheath of muscle bundles,

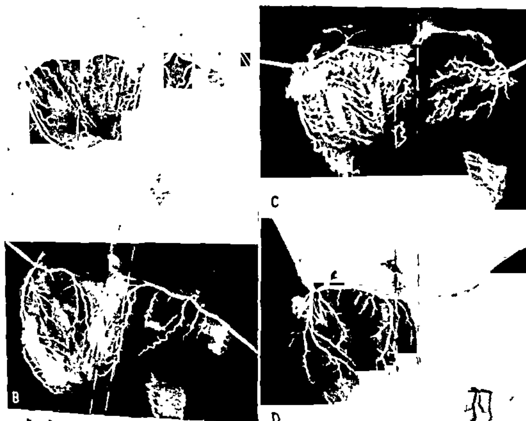


Fig 1-45 The coronary arteries of three common human types and the usual canine type, demonstrated by Schlesinger's method of "unrolling" the heart *after injection* with colored opaque solutions at controlled *pressures* A Coronary arteries of a human heart of group 1, i e, with the right coronary artery *preponderant* in the cardiac blood supply B Coronary arteries of a h... heart of group 2, i e, with a balanced circulat... group 3, i e, with ... arteries of ... ...roup 3. (from Schlesinger, Ame... ...ancement of Science, 1940)

and thymus area. Hypothetically, these may be of help in revascularizing an ischemic heart.

BLOOD SUPPLY OF THE CONDUCTING SYSTEM. The SA node in man is usually supplied by a large branch which enters the node and runs through its center while giving lateral branches which anastomose with vessels in the adjacent atrial muscle. This *artery of the SA node* is a branch of the artery of the ostium of the superior vena cava. In turn, this artery is nearly always a branch of the right coronary artery which arises near its ostium as one of the first anterior atrial arteries. This vessel ascends over the front of the right auricular appendage to reach the sulcus between the ostium of the superior vena cava and the base of the appendage on the roof and posterior wall of the right atrium This pattern is present in more than 70 per cent of hearts, and in 25 per cent of the cases, the principal stem of the artery of the ostium of the superior cava arises from the end of the left coronary artery as a branch of the circumflex branch of the left coronary artery when it forms the posterior descending artery. In some of the other hearts, the artery of the SA node arises from both coronary arteries. In rare cases, there is no distinct vessel to be identified.

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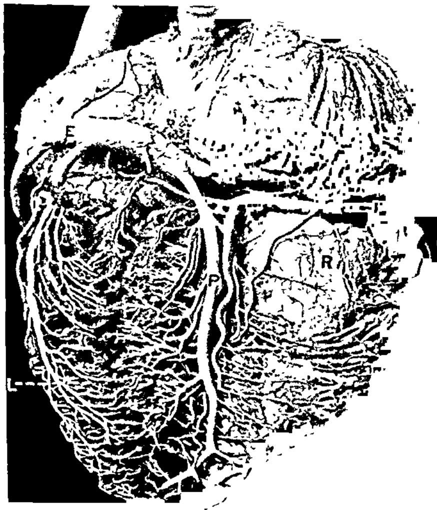


Fig. 1-44. Posterior view of celluloid cast of heart from a child, aged 14 years The left ventricle is markedly more vascular than the right *R* indicates the right ventricle; *L*, the left ventricle, *P*, the posterior interventricular vein; *E, the left coronary artery, F,* the right coronary artery (*From Whitten,* 1930)

essentially the same in normal hearts of rabbits and dogs This arrangement of capillaries as parallel channels between the muscle fibers enables a short cylinder of tissue around each capillary to be nourished and drained by it The evidence indicated that the apparently optimal concentration of capillaries remained essentially the same throughout life in normal hearts, although there was multiplication or increase in the number of capillaries during the period of normal growth, as would be necessary to maintain the same concentration with the increase in heart size of normal physiologic growth The increase in heart weight was directly proportional to increase in the average diameter of the muscle fibers, which in infants or children were quite small (8 6 μ or less) In the hearts of infants, there was a fiber to capillary ratio of as much as 5 9, with a gradual decrease during physiologic growth until a ratio of approximately 1 1 was reached and maintained throughout adult life regardless of heart size or disease (Fig. 1-48).

The conclusion reached was that the capillaries increased in number during the period of normal growth to maintain the optimum concentration at which one capillary at birth supplies four to six very small fibers, with a diameter as small as 6 μ Quite a different phenomenon occurs during the enlargement of the heart in response to heart disease with hypertrophy. *In the hypertrophied heart, the concentration of the capillaries decreases with increase in the*

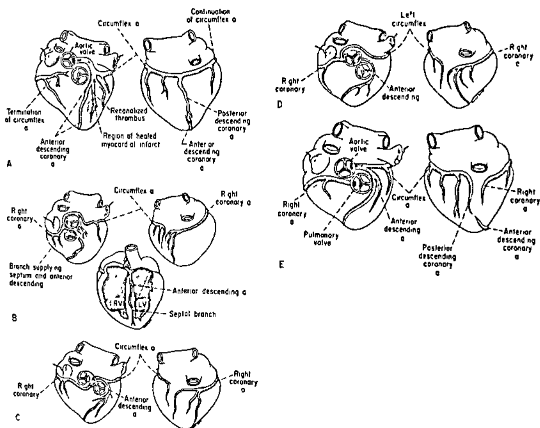


Fig 1-47 Variations in origin of coronary arteries from aorta A Single coronary artery arising from left aortic sinus and encircling the heart. Seventy-seven-year old man B. Single coronary artery arising from right aortic sinus and giving rise to the right coronary and left circumflex coronary arteries Anterior descending artery arises from right coronary artery and gives off a septal branch. Thirty-nine-year-old man C Origin of both coronary arteries from left aortic sinus Seventy-seven-year old man D Origin of left circumflex coronary artery arising from right coronary artery Eighty-one-year-old man E Origin of right coronary artery from pulmonary trunk usually symptomless In this heart the right coronary artery arises from the pulmonary trunk The left coronary artery arises from the aorta (*From Edwards, Atlas of Congenital Anomalies. Thomas, 1954* Courtesy of author and publisher)

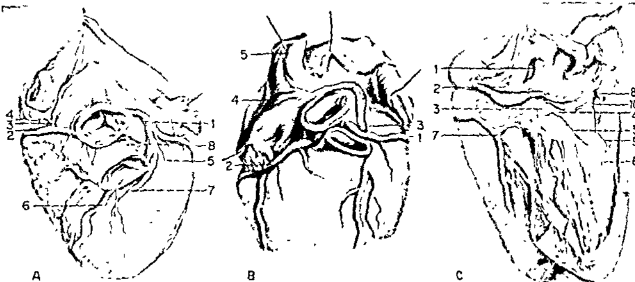


Fig. 1-46. Blood supply of the conductive tissue A. Sinoatrial node artery, 3, arising from right coronary artery, 2 B Sinoatrial node artery, 4, arising from atrial branch, 3, of left coronary artery, 1. C Artery of AV node, 3, coming from circumflex branch of left coronary artery, 7. Artery of AV bundle and right branch, 4 and 5, arising from right coronary artery, 10. (From Crainicianu, 1922)

usually at a perpendicular or oblique angle. From the branching arterioles, a network of capillaries is formed which wraps the individual muscle fibers in a basket-like covering of small capillaries These capillaries make a plexus whose meshes are usually an elongated trapezoid, the long sides of which are parallel to the long axis of the muscle fibers Between the capillaries, and parallel to the muscle fibers, are anastomosing capillaries which pass at an oblique angle across and around the muscle bundles, especially near the branching muscle fibers

The walls of the capillaries are, in general, smooth and are more or less parallel, as seen in longitudinal section There are irregular slight indentations and scallopings of the lumen which are minimal in comparison with the deep indentations and wide fluctuations in caliber characteristic of the cardiac sinusoids. As seen in transverse section, most of the capillaries are smoothly circular or oval in outline, but many of them are collapsed with irregular contours when empty and compressed by adjacent muscle fibers

Most of the capillaries are filled with blood cells, one or two or more columns in width, as contrasted with the arterioles, which are usually empty In some areas, however, the capillaries may appear empty or filled with plasma because of the plane of section passing between adjacent red cells It is possible that some capillaries are closed by spasm of the arterioles feeding an area in a cycle, allowing for rest of some areas as well as providing a reserve to meet greater demands or loss of some units, as has been demonstrated in the vascular units of the kidney and lung, but the proof of this is indirect and incomplete The typical arrangement of the capillaries, as seen in cross section of muscle bundles, is a rather uniform dispersal in the interstitial tissue between individual muscle bundles

The number of capillaries visible in the uninjected heart is much less than the number visible after the heart has been injected by a relatively diluted material capable of penetrating such small channels Because of the compression and emptying of the soft-walled capillaries by the forces of rigor mortis, as well as by runoff through arteriolumnal channels, many areas of heart muscle will have little or no injection of the capillary bed unless the injection of the cardiac vessels is made while the organ is viable and contracting rhythmically This method of completely filling the capillary bed was developed by Wearn (1928b). Later, Roberts and Wearn (1938, 1941) injected a large number of human and animal hearts by such a method, with abrupt stoppage of cardiac contraction when potassium chloride was substituted for the injected dye Using this method, they found the average supply to be about 3,342 capillaries per cubic millimeter in normal adult human hearts which had an average muscle fiber diameter of 13.9 μ and a ratio of one capillary for each muscle fiber Apparently this number reflects the optimal concentration of capillaries in normal human hearts, for such a concentration was found in all normal human hearts despite variation in age from a newborn state to extreme old age. The findings were

(Roberts and Beck, 1941) or by atrophy of emaciating diseases, the concentration of capillaries is increased (to as much as 4,946 capillaries per square centimeter), as expected with the decrease in average muscle fiber diameter and with maintenance of the same fiber to capillary ratio

In *hypertrophy with heart failure*, the majority of the capillaries are small in diameter, with apparent compression by the hypertrophied muscle fibers, a factor which further contributes to ischemia and failure of hypertrophied heart muscle. Roberts and Wearn (1941) presented formulas for predicting fiber diameter and vascularity from known heart weights

The *sinusoids* are vessels which are ordinarily overlooked but have been given importance by several authors (Wearn, 1936). Like sinusoids in other organs, these vessels are similar to capillaries in that they have a simple wall of endothelium and a few loose connective tissue fibers. They differ from capillaries in having a lumen which varies in diameter and contour throughout its length. In places, a sinusoid may be expanded into a space many times the diameter of a capillary (for example 30 to 200 μ in diameter), while in other areas, the sinusoid may be constricted in an irregular way with some protrusion of endothelial cells into the lumen The sinusoids communicate with capillaries or with arterioles and venules at either end In some places, sinusoids communicate with the lumen of the heart through the thebesian vessels (Fig 1-40).

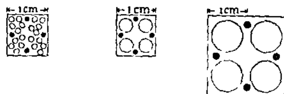
In addition to the network of capillaries and sinusoids described in the muscle bundles, there are other looser, or more scattered, capillary networks in the connective tissue planes between the adjacent large muscle bands Other capillary arrangements are found in the subendocardium and in the pericardium, as well as in the valves, pericardium, chordae tendineae, layers of the pericardium, tela adiposa, and in the walls of the coronary vessels, as well as in the aorta, pulmonary artery, and veins at the base of the heart. It is possible that these capillary beds in such areas, which appear to be scanty in the ordinary heart, may become dilated with functional significance as collateral anastomosing channels under certain stimuli of differential pressure gradients

The concentration of the capillaries in the conductive tissue is believed to be more abundant ... the nerve plexuses and ganglia which are distributed in several parts of the heart, most abundantly in the region of the SA and AV nodes and near the coronary arteries.

The Coronary, or Cardiac, Veins. The coronary veins, with the role of draining the cardiac capillary bed, are distributed throughout the heart in arrangements which more or less resemble those of the distributing channels of the coronary arteries. With the coronary arteries and capillaries, the *coronary veins* make a third arteriocapillary-venous system (in addition to the aortic and pulmonary systems) which begins on one side of the heart and ends at the other and, like the other two systems, will be affected by disturbances of gradients of pressure and oxygen saturation, as in forward or backward heart failure (Roberts, 1941).

THE ORIFICES OF THE CORONARY SINUS AND VEINS. The *coronary sinus* usually enters into the right atrium on its posterior wall through a ... ing is "guarded" by a thin endocardial reflection known as the *thebesian valve* on the right wall of the orifice between it and the opening of the inferior vena cava Occasionally, this valve is much larger, with long delicate strands extending up toward the orifices of the two venae cavae and known as the *network of Chiari*. The orifice is cranial or superior to the posterior cusp of the tricuspid valve, whereas above or to the left of the orifice are the interatrial septum, orifice of superior vena cava, fossa or foramen ovale, crista terminalis, and right auricular appendage (Fig 1-51).

The *accessory coronary veins*, 3 to 12 in number, open into the lower anterior wall of the right atrium by oval or round orifices about 1 to 2 mm in diameter. Other small orifices are present in other areas of the two atria and are most abundant on the right and left sides of the interatrial septum and on the posterior and left walls of the left atrium Usually several of these openings approach 0 8 mm in diameter. Most of the others are pinpoint or less in size, and many can be demonstrated only by use of injection or inspection with magnification, unless studied in stained sections and



13gm	300gm	900gm
6μ	14μ	28μ
3700	3500	1800
5F:1C	1F:1C	1F:1C

Fig. 1-48. Distribution of capillaries in normal infant and adult normal and hypertrophied human hearts (left to right) From above down are given typical data· (1) heart weight, (2) average muscle fiber diameter, (3) average number of capillaries per square centimeter, and (4) average fiber-to-capillary ratio. (*Based upon data of Roberts and Wearn. Am Heart J.* 1941)

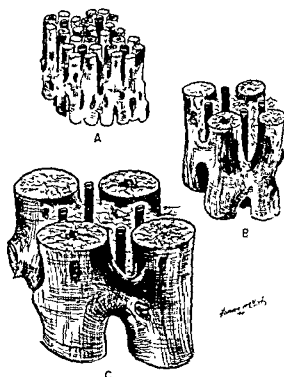


Fig. 1-49. Vascular changes in heart muscle attending growth and hypertrophy. A. From a newborn heart with normal concentration of capillaries, each supplying about six small fibers. B From a normal adult heart with the same concentration of capillaries in the ratio of one fiber for each capillary C. From a hypertrophied heart with a low concentration of capillaries which have not multiplied with increased size of fibers (*From Roberts in Sodeman's Pathological Physiology and Mechanisms of Disease* Saunders, 1950.)

diameter of the muscle fibers and heart weight. With hypertrophy in adult hearts, regardless of age or cause, there is ischemia at the capillary level in direct proportion to the degree of hypertrophy.

In hypertrophied human adult hearts with an average weight of 538 Gm, the average diameter of the muscle fibers was 20 μ or more with about 2,400 capillaries per cubic millimeter while the ratio of fibers per capillary remained 1.24 In the largest hearts, of 1,000 Gm, the muscle fiber diameter reached 36 μ, and the capillaries fell to 800 per cubic millimeter (Figs 1-49, 1-50) Using these measurements, the average capillary surface area available for supplying 1 cm^3 of muscle fiber tissue was found to be 882 cm^2 for children's hearts, 787 cm^2 for the normal hearts of adults, and 585 cm^2 for the hypertrophied hearts. With hypertrophy 94 per cent of the volume of cardiac tissue is composed of muscle, compared with 67 per cent in normal adult hearts and 77 per cent in normal children's hearts There was a wide range in normal hearts for the capillary surface area per cubic centimeter of contractile muscle tissue (average 1,184 cm^2 for normal adult hearts), but all the hypertrophied hearts fell in a range well below the lowest of the normal (with an average of 625 cm^2). These concepts are easy to correlate with the loss of cardiac reserve which is apparent in hearts that have been diseased enough to cause hypertrophy.

With *atrophy of the heart muscle,* on the other hand, whether caused by constrictive pericardial disease with "atrophy of disuse"

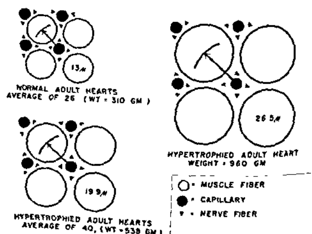


Fig. 1-50. Diagrams of the relationship of myocardial fibers, capillaries, and nerves in normal and hypertrophied human hearts With hypertrophy the muscle fibers become ischemic, but the terminal nerve fibers remain close to the capillaries (*From Roberts,* 1945)

serial section reconstructions. In the atria, most of these belong to the venoluminal system or thebesian veins Some of the openings in the endocardium of the right and left ventricles are also of the venoluminal system, as seen by demonstration of their connections with tributaries of either the accessory coronary veins or the coronary sinus Estimates of the number of such orifices of the coronary arterioveno-luminal system vary according to the technique used for demonstration and the criteria for nomenclature Such estimates vary from 5 to 30 in the ventricles and 20 to 80 in the atria for vessels demonstrated by injections or inspection with magnification. The number is much greater if openings visible only in histologic sections are included. Efforts to increase these arterioluminal openings by making 30 to 50 endocardial punctures in the left ventricle led Roberts (1956) to suggest this as another way to revascularize the heart.

THE CORONARY SINUS This largest of the cardiac veins has become well known in recent years since its use for revascularizing the ischemic heart by arterialization was reported by Roberts (1938–1945). The sinus, which is usually a little smaller than a person's little finger, extends from the orifice of the coronary sinus on the back of the right atrium toward the left, or obtuse, margin of the heart. In a normal adult human heart, it is about 3 to 5 mm in diameter and 2 to 5 cm in length Its left, lateral or proximal end lies variably on the left poste...

... sulcus, where it may bulge and be readily visible when the heart is rotated out of its bed during life In patients who have had severe congestive heart failure, especially those with right atrial hypertension or with large hypertrophy of the heart, the sinus may be several times the average normal diameter, with a widely patent orifice

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...agnosis, therapy, or analysis of mechanisms On the anterior wall of the coronary sinus, passing from its orifice on the right to its origin at the left end, are the endocardium and cardiac muscle of the posterior wall of the right atrium, the AV node and bundle, the posterior edge of the interatrial septum, the endocardium and cardiac muscle of the posterior wall of the left atrium, and the left circumflex coronary artery near the origin of the sinus.

THE CORONARY SINUS DIMPLE. A prominent dimple or funnel-shaped depression is found in the angle just above the orifice of the coronary sinus and to the left of the end of the inferior vena cava. In the dog's heart it is more conspicuous than in human isolated hearts, where it is often filled with fat. As described by Roberts (1958), it is a very useful landmark for the orifice of the coronary sinus or the site of the AV bundle.

TRIBUTARIES OF THE CORONARY SINUS. Several posterior right and left coronary veins drain the posterior walls of the right and left atria and empty into the upper edge of the coronary sinus, they average about 0.1 to 0.5 mm in diameter They anastomose abundantly with each other and with the thebesian veins, as well as with anterior coronary veins over the upper and anterior surfaces of the two atria and auricular appendages. A fairly large right posterior ventricular vein drains the acute margin and posterior surface of the right ventricle and runs a rather horizontal course, approaching the posterior AV sulcus at a slight angle, until it ends by emptying into the extreme right end of the coronary sinus on its floor or posterior wall near the thebesian valve of the coronary sinus. Just to the left of this point is a prominent dimple or funnel-shaped depression which is an important landmark in identifying the orifice and end of the coronary sinus. Two or three larger posterior ventricular coronary veins empty into the floor or lower part of the anterior wall of the coronary sinus. They lie in the subepicardial fat on the posterior surface of the interventricular septum and left ventricular wall They are formed by the union of numerous smaller tributaries which approach each other at a sharp acute angle superficial usually to the branches of the associated coronary arteries. They cross superficial to the terminal trunk of the posterior circumflex and descending coronary arteries, whether formed from either the left or the right coronary artery.

Also found crossing from below upward on the anterior wall of the coronary sinus are several branches of either the left circumflex coronary artery or the terminal part of the right coronary artery and, of course, the plexus of nerve cell bodies, ganglia, and fibers of the myocardial cardiac

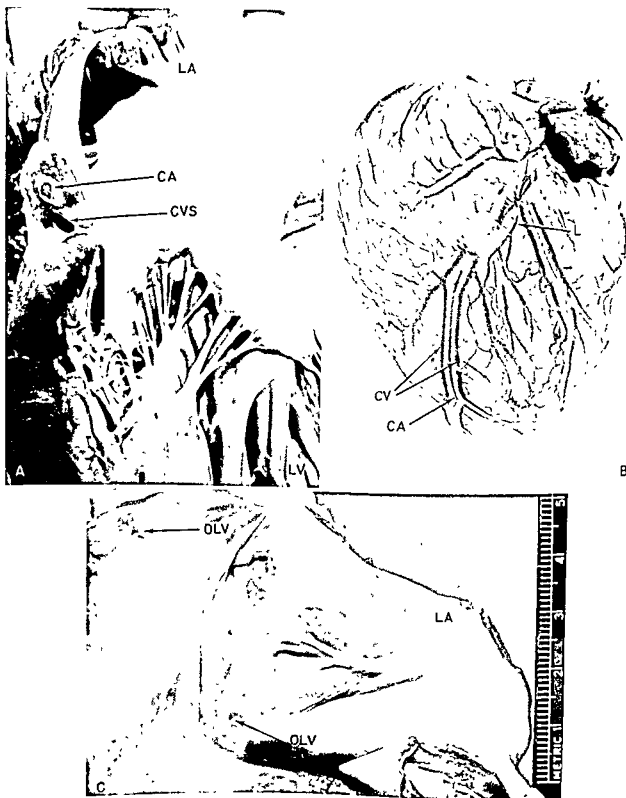
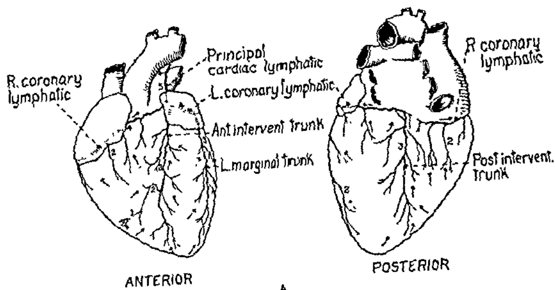


Fig 1-51. A Important relations of coronary venous sinus, *CVS*, and left circumflex coronary artery, CA, to the mitral ring The artery contains a clot B Epicardial lymphatic vessels, visualized quickly after injection of india ink into the myocardium of a beating dog's heart The large anterior coronary lymphatic trunk (at *L*, marked by arrow point) crosses superficial to the paired broad, dark coronary veins, CV, and the lighter-colored coronary arteries, CA The accessory coronary veins and some noninjected lymphatic vessels are shown also A muscular bridge crosses the anterior coronary vessels C. Orifices, *OLV*, of several thebesian or luminal vessels, in left atrium, *LA*, of adult human heart, marked by arrows (*From Roberts, 1945*)



epicardium
myocardium
endocardium
B

Fig. 1-52 A *Diagram of the anterior and posterior surfaces of the dog's heart showing the course of the principal lymphatic trunks* Vessels of the first, second, third, fourth, and fifth orders are indicated by the figures 1, 2, 3, 4, and 5 Arrows indicate the direction of lymph flow. ×½ B. A schematic drawing of a section of the ventricular wall of a dog's heart, illustrating the relationship between the subendocardial, myocardial, and subepicardial lymphatic plexuses and the relation of the myocardial lymphatic vessels to the muscle bundles and arteries (white) and veins (stippled). Approximately ×12. *(From Patek Am. J. Anat. 1939.)*

plexus. On the posterior wall of the sinus are the subepicardial connective tissue and fat, the visceral pericardium or epicardium, the pericardial space, the parietal pericardium, and units of the posterior mediastinum, left lung, and posterior body wall, as well as the descending aorta and esophagus and sympathetic chain. On the roof or superior wall of the coronary sinus, besides the fusion of the anterior and posterior relations are two to five posterior right and left atrial veins emptying into the sinus, a frequent but not constant extension of right atrial muscle which passes over the roof and on the posterior wall of the sinus, and the right and left inferior pulmonary veins On the floor, as inferior or caudal relations of the sinus, are the posterior part of the right AV (tricuspid) fibrous ring and posterior tricuspid leaflet, terminal branches of the right coronary artery forming the posterior right circumflex or posterior descending coronary arteries, and the left circumflex coronary artery, if it extends this far on the posterior surface of the heart. The left circumflex coronary artery is an important relation in the hearts of most dogs and a small percentage of the human hearts which have a "left coronary artery–predominant pattern" (Fig 1-45).

Similar veins are seen on the obtuse margin of the left ventricle and unite to form one or two larger channels about 1 mm in diameter These end in the origin, or left end, of the coronary sinus by fusing with the one or two large anterior coronary veins which parallel the left anterior descending coronary artery On each side of the latter is a vertically placed vein which receives tributaries from the area of the right ventricular anterior and apical wall and infundibular region adjacent to the interventricular septum, and from the left or lateral anterior wall of the left ventricle, as well as deep or penetrating veins draining the anterior and apical edge of the interventricular septum These veins fuse in the triangle between the angle of bifurcation of the left common coronary artery trunk to form a single large vein about 2 mm in diameter, known as the *great cardiac vein*. This vessel also receives a large anterior atrial septal vein, which leaves the anterior edge of the interatrial septum. After draining the vasa vasorum of the root of the aorta and pulmonary artery and their valves, it passes over the left coronary artery and under the left auricular appendage. From this point of fusion, the great cardiac vein runs to the left and then posteriorly in the AV groove until it forms the left end of the coronary sinus At this point, there is frequently a small valvelike fold of the endothelium at the left end of the coronary sinus. This "inner valve of the coronary sinus," or *valve of Vieussens*, is usually incompetent but occasionally may be quite sizable and possibly of use in preventing regurgitation or catheterization beyond the coronary sinus. Similar flimsy folds of endothelium may resemble valves at the orifices of the other tributaries of the coronary sinus, but elsewhere in the coronary veins there are no valves Near their junction the coronary sinus or great cardiac vein may receive a more prominent left posterior atrial vein known as the *vein of Marshall* This vessel occasionally is quite prominent as it descends over the roof and posterior wall of the left atrium between the left and right pulmonary veins while it slants from above and on the left downward to the right toward the origin of the coronary sinus. Usually of no importance, this channel is rarely of great significance as a congenital anomaly, receiving a persistent left superior vena cava or pulmonary vein.

ANTERIOR ACCESSORY CORONARY VEINS. These veins are usually seen in most hearts but are generally ignored. Although described by Grant (1940) and others, their magnitude and potential significance are ignored These anterior accessory coronary veins, three to six or more in number, drain the upper right portion of the wall and acute margin of the right ventricle, as well as part of the conus or infundibular region They drain into the lower edge of the anterior wall of the right atrium, a few millimeters above the anterior tricuspid valve leaflet, usually as single openings, but occasionally they empty into the upper edge of the right ventricle wall below the valve (Gregg, Shipley, Pritchard, and Bidder, 1943, 1947) These accessory veins anastomose freely with the thebesian channels, the right anterior coronary veins, which drain into the great cardiac vein, and a prominent plexus of coronary veins with large irregular meshes surrounding the vortex of heart muscle at the apex (Fig 1-51).

MINIMAL CARDIAC VEINS OF THEBESIUS These small vessels (*venae minimae cordis*), as indicated above, connect their orifices in the endocardial surface of the cardiac chambers with the venules, capillaries, and sinusoids of the myocardium, and probably at times directly with small arterioluminal vessels and arterioles.

to the blood capillaries in the interstitial spaces between adjacent muscle fibers and drain into larger lymphatic channels which follow the venules to the interstitial connective tissue septa. From here they drain toward the epicardium

The *epicardial plexus of lymphatic channels* draining the myocardial and subepicardial plexuses of lymphatic vessels is a loosely arranged plexus in the subepicardial connective tissue. These small lymphatic channels drain into several rather constant lymphatic channels of larger size.

The *principal lymphatic drainage channels* of the heart are the only part of the system grossly visible without special methods of study. If the heart is inspected closely, especially when fresh, or alive and beating, or with magnification, special injections, or sections, several large lymphatic vessels are seen The most conspicuous is a fairly large channel, glistening and transparent like a fine silk thread and lying parallel and superficial to the anterior descending coronary artery and veins known as the *anterior cardiac lymphatic trunk* Near the apex, this is made of two or three channels on either side of the artery which then fuse near the conus into a single channel

The larger *anterior middle cardiac lymphatic trunk* usually runs up toward the base of the conus region, a millimeter or two to the right of the anterior descending coronary artery. Here it joins with the *right anterior ventricular lymphatic vessel*, which begins on the right part of the posterior wall of the right ventricle and acute margin of the right ventricle and runs first anteriorly and then to the left a few millimeters inferior to the AV groove in the subepicardial fat across the front of the right ventricle. After going across the front of the infundibulum to join the ascending *anterior middle cardiac lymphatic vessel*, the right cardiac lymphatic trunk then passes to the left of the valve of the pulmonary artery, superficial to and above the trunk of the left coronary artery. At this point, it receives its other main tributary, the *left anterior ventricular lymphatic vessel* The latter runs in the subepicardial fat superficial and anterior to the left circumflex coronary artery and the great vein of the heart. It is formed by the union just below the origin of the coronary sinus of ascending lymphatic vessels from the obtuse margin of the heart with those from the posterior surface of the left ventricle. In the posterior interventricular sulcus, a fairly constant large channel, the *posterior ventricular lymphatic vessel*, parallels the posterior descending artery near the apex but turns upward and to the left as it approaches the AV sulcus *Thus, all the lymphatic vessels draining the subepicardium, the myocardial plexus, and the subendocardial plexus unite in a single common lymphatic trunk*, which crosses the top of the left coronary artery under the arch of the main pulmonary artery and left pulmonary artery, passing to the left of the aortic valve, and leaves the pericardium to join a left mediastinal plexus of vessels. Eventually this trunk and all its tributaries are thought to drain into the mediastinal lymph nodes, which in turn drain through the thoracic duct to the left jugular subclavian bulb and return to the blood vascular reservoir. At times, a second large posterior lymphatic trunk may drain separately to the hilar nodes (Patek, 1939).

The myocardial and epicardial lymphatic vessels can be demonstrated readily by injecting india ink or other material through a small sharp needle into the substance of the beating myocardium. Within the brief interval of two or three heart beats, the myocardial and subepicardial lymphatic vessels are visualized, indicating that the lymphatic flow in the beating heart is of considerable volume and of a fairly high rate of flow (Roberts). This rapid filling of epicardial lymphatic vessels often was seen also in contusion of the heart or after implanting the open end of the subclavian or other artery into the myocardium. Simple ligation of cardiac lymphatic vessels seemed to cause little change unless the veins were also ligated, producing distention and stasis (Roberts, 1958). Cannulation of the common lymphatic trunk indicates that this rate of flow is about 4 to 20 ml/min in the normally beating heart of a small dog (Drinker et al, 1940).

The *pericardial lymphatic plexus*, less often described, is a loosely organized plexus of lymphatic channels and capillaries in the loose connective tissue of the outer layer of the parietal pericardium. This plexus receives small drainage also from the lymphatic plexus in the pericardial reflections around the root of the aorta, pulmonary artery, superior and inferior vena cava, and pulmonary veins. The pericardial plexus drains to the lymphatic channels in the anterior mediastinum (then upward

Many of them are very short trunks which pass only through a very short distance of the endocardium after being the union of small tributaries in the subendocardium and inner few layers of the myocardium. They make thus a small structure resembling an *arbor vitae* when visualized by injection of dye through a blowpipe placed over the orifice (Grant and Viko, 1929). Others penetrate longer distances toward the epicardium A third type runs predominantly in plexuses parallel to the luminal endocardium. Each of these thebesian veins has capillary and venular tributaries. As some of these channels penetrate the endocardium at a sharp angle, a fold of endocardium may form an apparent valve which may inhibit partially the reflux of blood from the cavity into myocardium.

INTRAMYOCARDIAL AND PERICARDIAL PLEXUS OF CARDIAC VEINS AND VENULES. Throughout all parts of the myocardium is a plexus of veins anastomosing with each other in all directions. In the smaller muscle fiber bundles, venules form from the union of capillary meshes and run transversely or obliquely across the fibers to reach the interfascicular connective tissue planes. Here the venules join others to form a plexus in these septa for variable distances before sending some larger veins to the surfaces of the heart as tributaries of either the coronary veins and its trunks, the accessory coronary veins, or the venoluminal channels In the parietal pericardium, a few veins of small diameter drain the sparse capillary bed of the pericardium. These veins are most abundant in the regions of the phrenic nerves, over the conus and the diaphragm, and near the pulmonary veins Minor anastomoses occur with the tributaries of such nearby veins as the internal mammary, superior epigastric, superior phrenic, pulmonary, esophageal, and paravertebral veins.

ANASTOMOSES OF THE CARDIAC VEINS Besides those just named between veins of the pericardium and veins of the superior, anterior, and posterior mediastinum, anastomoses of the cardiac veins include those between tributaries of the coronary sinus and of the anterior accessory coronary veins at all levels of size, between these two groups and the thebesian veins, and rare anomalies occurring as communications between the coronary sinus or vein of Marshall and a left superior or inferior vena cava, or even pulmonary veins. These are vestiges of the left cardinal veins and duct of Cuvier.

The Cardiac Lymphatic Vessels. The lymphatic system of the heart is usually given no attention. It is an abundant system, however, which can be demonstrated easily with appropriate magnification and injections It consists of the four cardiac subdivisions to be described, in addition to a fifth section draining the parietal pericardium and great vessels at the base of the heart (Figs. 1-51B, 1-52A, B).

The *subendocardial plexus* is a plexus of small lymphatic channels forming a branching and anastomosing network with large meshes, lying in the subendocardial connective tissue layer of all four chambers of the heart

These channels are difficult to demonstrate except with injections and on histologic sectioning. In such sections, the lymphatic channels may be distinguished from the blood vascular channels after the latter have been injected with dye The subendocardial plexus drains into the myocardial plexus through small channels which have no characteristic pattern. A potential space, probably filled with lymph, surrounds many parts of the AV conduction system in some hearts and at times is referred to as the lymphatic space around the Purkinje cells and other parts of the conductive tissue (Robb et al., 1937). Around the lower part of the AV node, and extending prominently around the AV bundle and its proximal right and left branches, is a larger space with a sheath of loose connective tissue and apparent endothelial cells, known as the *sheath of Curran* The sheath of Curran is prominently developed in the hearts of ungulates, in such specimens, it is easy to visualize graphically the conduction system by injection of india ink or other opaque material through a needle inserted in the sheath of Curran. In the hearts of human beings, dogs, and other animals which are more likely than the ungulates to receive medical interest, such a sheath is difficult to visualize because the space is irregular and scanty. It may not be accurate to refer to the sheath of Curran and its extensions around the terminal arborization branches of the Purkinje network as lymphatic channels (Roberts, 1937b)

The *myocardial plexus* is a more voluminous plexus of lymphatic capillaries and small channels which form a network very closely similar to the blood vascular plexus of capillaries and venules throughout the myocardium. They form a basket-like network of lymphatic capillaries around the branching and anastomosing myocardial fibers. The lymphatic capillaries lie close

lying visceral pericardium, a layer seen also on the branches of the coronary arteries which lie on the surface of the heart

In the intima of the coronary arteries, especially the larger ones, there is a rich plexus of subendothelial or intimal blood vessels, the *intimal vasa vasorum*. Although not described by many investigators, these channels have been clearly demonstrated by Winternitz et al. (1938), as well as others The intimal vasa vasorum (demonstration may require injection of the vessel during the fresh state, with fixation while the injection mass is under pressure) usually originate directly from the lumen of the parent vessel but may arise from the lumen of branches of the vessel as the wall of the branch passes through the wall of the larger vessel These several types of intimal vasa vasorum anastomose to some extent with each other and also with the vasa vasorum in the media and adventitia.

The vasa vasorum of the coronary arteries are exaggerated in the area around an atheromatous plaque. This has given rise to much debate as to whether such plaques may be the result of deposits in dilated vasa vasorum in the area where such vessels have ruptured or been injured, or, on the other hand, whether such dilated and prominent vasa vasorum represent the local reaction to an injury by an atheromatous or other lesion

Within the wall of the coronary arteries of all sizes, but especially prominent near the adventitia of the larger and middle-sized coronary arteries, there are numerous nerve fibers and nerve cells These nerve fibers form richly branching and anastomosing plexuses, chiefly in the adventitia but extending into the media with ramifications about some of the smooth muscle fibers and vasa vasorum Some of these fibers are of middle size with relatively thick myelin sheaths, whereas probably many more have little or no myelin sheath

The intramyocardial, penetrating, and other unnamed small branches of the coronary arteries are progressively much smaller in diameter with relatively thicker walls in proportion to the diameter of the lumen than in the major coronary arteries, where the diameter of the lumen and the thickness of the vessel wall are [illegible] the larger coronary arteries, but in some hearts, this may be much thicker than in others; in such cases it may be impossible to rule out proliferation by disease, stress, or other mechanisms. The internal elastic lamina is also less conspicuous but is still a detectable layer, whereas the external elastic lamina and other elastic layers are much less evident. The adventitia of these vessels also appears less well organized as a circular layer but blends imperceptibly with the loose connective tissue structures of the septa nearby.

The capillaries and sinusoids of the cardiac blood vascular and lymphatic systems consist of delicate structures with very thin walls and relatively wide lumen The wall typically is comprised of only a single layer of endothelial cells with two or three loosely arranged fibers of connective tissue surrounding this tubule. At rare intervals, cells of Rouget (which resemble smooth muscle fiber cells) may be applied to the surface of the capillary. The circumference of the capillaries comprises about one to five endothelial cells, whereas in the larger sinusoids, there may be 20 to 50 or more endothelial cells of irregular shape around the circumference. Aside from being much more dilated and changing in diameter, the sinusoids resemble the capillaries in microscopic structure. The lymphatic capillaries are similar in structure to the blood capillaries and run closely parallel to them, so as to form a basket-like network around the muscle fibers They usually contain no red blood cells and will be free of dye injected through the coronary arteries to visualize the hemic capillaries. The lymphatic capillaries are abundant also in the walls of the larger coronary blood vessels

The neuroanatomy of the coronary vessels, as of the heart as a whole, is very poorly understood, as to both structure and functional organization This is because of the difficulty in distinguishing artifacts from such small nerve fibers It is easy to demonstrate numerous nerve fibers and nerve cells in the walls of all the coronary arterial, venous, and lymphatic systems, regardless of size These are believed to be branches of both the vagus and sympathetic nervous system, some sensory and some motor in type Even the smaller *nervi vasorum* have blood vessels of their own (or *vasa nervorum*), indicating the closely associated function of the blood vessels and nerves. Within the myocar-

along the internal mammary artery to the clavicular lymph nodes, to the right lymphatic trunk, and the thoracic duct on the left), through the lymphatic vessels on the upper surface of the diaphragm and in the wall of the esophagus and posterior thoracic wall, eventually to the thoracic duct also

HISTOLOGY AND NEUROANATOMY OF THE CARDIAC VESSELS

The normal anatomy of these vessels resembles in microscopic structure that of vessels of similar size elsewhere in the body (Gould, 1953, Gross et al., 1934, Ehrich et al, 1931). The coronary arteries are possibly more predisposed to atherosclerotic and fibrinoid diseases (as in the collagen diseases) than are most vessels elsewhere, however, it is possible that this inference is only due to the dramatic nature of such involvement.

The main coronary arteries, as they leave the wall of the aorta and for some distance down the branches, have the characteristics of the so-called "middle-sized arteries," in distinction from the large elastic arteries (such as the aorta and its largest branches), and the small arteries or arterioles In the latter group are the penetrating and myocardial arteries of the heart. In a similar way, the veins and lymphatic channels of the heart resemble histologically such structures elsewhere

The right and left coronary arteries and their principal branches are "muscular" arteries with relatively thick media composed of many layers of smooth muscle, chiefly arranged in a circular manner. Between these smooth muscle fibers are strands and layers of white fibrous connective tissue, or collagen, as well as several thin layers of elastic connective tissue fibers and some reticular fibers The internal elastic lamina is very conspicuous in these vessels as a thick homogeneous wrinkled ring or lamina at the junction of the intima and media. The external elastic lamina is less conspicuous but often well developed. The adventitia of these coronary arteries is usually about half the thickness of the media and is made up of longitudinal and circular fibers of collagen, with occasional elastic and reticular fibers The adventitia has a rich plexus of small blood vessels of arteriole and capillary size, known as the *vasa vasorum*, which arise from the wall of the secondary branches of each artery as well as directly from the intima of the artery whose wall is being supplied. These vasa vasorum are most numerous in the adventitia, where they anastomose with small vessels in the adipose tissue and connective tissue surrounding the vessel. The intima of the named, or larger, coronary arteries is an important layer consisting of the endothelial lining of the vessel and the subendothelial layer of loose connective tissue and interstitial or ground substance The intima is made of mesothelial cells which are simple squamous epithelial cells. These are usually elongated, diamond-shaped cells which are flattened so that the two surfaces are almost in contact with each other, except for a slight bulging around the nucleus, which is placed somewhere near the center of the cell The cytoplasm is normally very thin The edges of the endothelial cells are irregularly scalloped or jagged as shown with special staining methods In the angles between the cells, there may be openings, or *stoma*, which are considered to be artifacts by some workers, or significant pores by others The subendothelial or subintimal layer is much thicker than the endothelial layer. Its normal thickness may vary from about one-twentieth to one-fifth the thickness of the media However, because of the great variation described by many workers regarding the thickness of this structure, it is difficult to discern whether the intima in an individual section is normal or abnormally thickened. For example, Dock (1940) believes the intima to be much thicker in the hearts of newborn male infants than in the coronary arteries of female infants; this has been confirmed by some (Moon, 1957) but doubted by many others

The *coronary venules* may closely resemble the arterioles, except that the layer of smooth muscle cells in the media is much less abundant and the elastic lamina is not present as an organized structure. The wall of the larger coronary veins and coronary sinus also has three layers, as in the arteries, but each of these is much thinner and less well supplied with elastic fibers, vasa vasorum, and nerve fibers In the wall of the coronary sinus, there may be some strands of cardiac muscle as well as the smooth muscle fibers The coronary sinus and the other coronary veins, where they lie on the surface, have a serosa on one edge because of the over-

As the large return of blood from the cephalic or anterior left cardinal vein is lost by being shifted to the right side through the superior vena cava, persistence of the left duct of Cuvier is maintained by fusion of several of its small tributaries or buds with venous channels which have been developing as drainage channels for the sinusoidal beds in the myocardium. Thus, by the time the stratum spongiosum of the myocardium has been relatively lost with the development of the thicker compact layer, the venous tributaries of the coronary sinus have developed to serve as its drainage from the two atria, the posterior wall of the right ventricle, and all the left ventricle The anterior wall of the right ventricle is drained by the accessory coronary veins, which open directly into the *right atrium* The *small* right coronary vein empties into the right end of the sinus just to the left of the orifice of the inferior vena cava Its origin is presumably the same as that of the other tributaries of the coronary sinus, however, one *might speculate that it is the vestigial remains of one of the tributaries of the* caudal or posterior right cardinal veins or tributaries of the right duct of Cuvier

During the period between the fifth and eighth weeks, the pulmonary veins are being formed nearby, first as a single *trunk draining the multiple* pulmonary veins into the left atrium dorsally. These multiple pulmonary veins have developed independently, *not by* conversion of old vascular channels, *so as to* drain the various branches of the lung buds. As the atrium *grows, the* single pulmonary vein trunk is absorbed into the atrial wall until usually *four* of its original branches come to open *directly into the* left atrium as the *main pulmonary veins of* the adult Less than the usual *amount* of resorption of the primitive common pulmonary veins or asymmetric absorption thereof may *result in* different numbers of pulmonary veins emptying into the left atrium. Because this *area* of the *anlage* is developing rapidly with *severe stresses* owing to the developing septa *of the* atria, ventricles and [illegible]

[illegible] becomes the coronary sinus, it is easy to see why *anomalies* in the formation of the coronary sinus *and* the pulmonary veins at this point are *possible* It is difficult to see why they are not *more* common, and *it is* probable that, with careful search of this area, more examples of pulmonary veins emptying into the coronary sinus will be found (Roberts). If the left anterior or cephalic cardinal vein persists as a permanent channel (as it occasionally does), there is a large left *atrial posterior vein* going obliquely across the back of the left atrium, known as the *vein of Marshall*, which is contained in a prominent fold of pericardium. When the vein atrophies, it becomes a fibrous cord in this pericardial fold known as *the ligament of Marshall.* This anomaly may result in a *persistent left superior vena cava*, opening into the end of the coronary sinus, or possibly into the left atrium. A much *rarer anomaly is* the *persistence of the left inferior vena cava,* opening into the lower part of the left end of the coronary sinus, or one of its tributaries, because of persistence of the left *posterior or* caudal cardinal vein (Figs. 1-53, 1-54).

The *3d phase* of development of the coronary arteries begins during the seventh week, when they first appear in embryos about 14 to 15 mm in *crown-rump* length. At this time, the *coronary* vessels are small channels with a

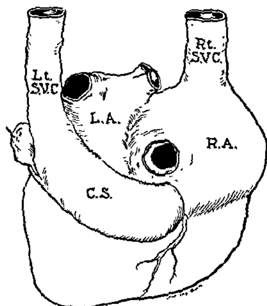


Fig. 1-53. Variations in the coronary sinus Diagrammatic representation *of heart* from behind. Persistent left superior vena *cava, Lt S.V.C.,* joins the left extremity of the dilated *coronary sinus, C.S.,* and the blood is carried into the *right* atrium, *R.A.* *L.A.*, left atrium, *Rt. S.V.C.*, right superior vena cava (From Burchell, 1948.)

dium, small nerve fibers may often be identified in the interstitial tissue between individual muscle fibers. These nerve fibers are closely associated with the cardiac capillaries in their plexiform arrangement. This close relationship of the capillaries to the terminal nerve fibers in the interstitial tissue, despite wide separation of capillaries with ischemia of muscle fibers during hypertrophy, seems a good explanation of the rarity of cardiac pain as a result of cardiac hypertrophy without other complications, in view of the finding that *ischemia of nerves is a factor in lowering the threshold for pain* (Roberts) With such a relationship, the myocardial nerve fibers would not be so ischemic as the muscle fibers in hypertrophy and therefore would not have their threshold of irritability lowered, although the muscle fibers were ischemic and predisposed to failure.

A nerve reflex arc from the cardiac nerves to somatic nerves in the chest wall, arm, or other area of referral has been proposed to explain "heart pain" or other sensory and motor disturbances after coronary stenosis (Roberts, 1945–1956). Ligating a coronary artery caused vasospasm of the vasa nervorum in the area of anginal referral.

EMBRYOLOGY OF THE CORONARY VESSELS

The development of the coronary arteries during fetal life has received little attention despite the large amount of study given to the development of the chambers and septa of the heart (Goldsmith and Butler, 1937, Patten, 1946, 1953) The several phases in the known development of the cardiac blood vessels are as follows: (1) initial phase of nourishment and drainage of the predominantly spongy wall of the heart by *sinusoids*, (2) development of the *coronary veins* by budding from the coronary sinus; (3) development of the *coronary arteries* by budding of branches from the aorta, (4) penetration of the developing compact myocardium by branches of the coronary veins and arteries; (5) compression of large sinusoids into *capillaries* with a few vestigial remains, as the spongy inner myocardial layer atrophies; (6) union of some cardiac capillaries with budding regional lymphatic channels to form the cardiac lymphatic vessels.

In *phase 1*, nourishment of the heart is entirely by transcellular diffusion and by large sinusoids between the widely spaced muscle fiber trabeculae of the spongy myocardium which makes up practically all of the wall of the heart muscle during the first 2 or 3 weeks of embryonic life. As the primordial cardiac tube grows with elongation and sinuous torsion on itself, the tube becomes hollowed out in the central axis by the forming of small capillary or sinusoidal spaces which enlarge, fuse, and unite with each other, with oscillating pulsations at first and then with a peristaltic pulsation, as a pacemaker is formed and the rhythmic beat becomes well established There is no doubt an ebb in flow, or *tidal circulation*, through these sinusoids and intertrabecular spaces, into which small capillaries open for both nourishment and drainage of the myocardium at this period prior to establishment of veins and arteries.

Phase 2 deals with the formation of the coronary veins As the atrium and sinus venosus become distinct chambers, at the age of about 2½ to 3 weeks (12 to 14 somites), with bulging of the atrium posteriorly and cranially behind and to the left of the truncus arteriosus, the *two cardinal veins* (right and left) are drawn into the proximal end of the sinus venosus With further growth of the atrium toward the right, as well as toward the left, the sinus venosus is absorbed into the wall and lumen of the right part of the atrium at its caudal edge. The right cardinal vein, or *duct of Cuvier*, is lost in the development of the right atrium, with its tributary limbs being left behind as the superior vena cava on the right with its innominate, common jugular, and subclavian tributaries growing out from the anterior right cardinal vein. The right posterior cardinal vein remains as the stem of the *azygos vein*. During this period, up to the end of about 3½ weeks (17 to 19 somites), the left common cardinal vein, or *left duct of Cuvier*, enters the right swelling of the atrium just to the right of where the secondary interatrial septum is being formed The left common cardinal vein at this time still has the anterior cardinal vein and the posterior cardinal vein (receiving the umbilical veins) as tributaries In the embryo by the end of the fifth week (6 to 8 mm, crown-rump length), the left common cardinal vein becomes correspondingly smaller as the right has become larger It crosses the dorsal wall in the posterior AV sulcus, which has been forming

As the large return of blood from the cephalic or anterior left cardinal vein is lost by being shifted to the right side through the superior vena cava, persistence of the left duct of Cuvier is maintained by fusion of several of its small tributaries or buds with venous channels which have been developing as drainage channels for the sinusoidal beds in the myocardium. Thus, by the time the stratum spongiosum of the myocardium has been relatively lost with the development of the thicker compact layer, the venous tributaries of the coronary sinus have developed to serve as its drainage from the two atria, the posterior wall of the right ventricle, and all the left ventricle. The anterior wall of the right ventricle is drained by the accessory coronary veins, which open directly into the right atrium. The small right coronary vein empties into the right end of the sinus just to the left of the orifice of the inferior vena cava. Its origin is presumably the same as that of the other tributaries of the coronary sinus, however, one might speculate that it is the vestigial remains of one of the tributaries of the caudal or posterior right cardinal veins or tributaries of the right duct of Cuvier.

During the period between the fifth and eighth weeks, the pulmonary veins are being formed nearby, first as a single trunk draining the multiple pulmonary veins into the left atrium dorsally. These multiple pulmonary veins have developed independently, not by conversion of old vascular channels, so as to drain the various branches of the lung buds. As the atrium grows, the single pulmonary vein trunk is absorbed into the atrial wall until usually four of its original branches come to open directly into the left atrium as the main pulmonary veins of the adult. Less than the usual amount of resorption of the primitive common pulmonary veins or asymmetric absorption thereof may result in different numbers of pulmonary veins emptying into the left atrium. Because this area of the anlage is developing rapidly with severe stresses owing to the developing septa of the atria, ventricles, and ostium atrioventriculare, in addition to the rotation of the cardiac tube with stretching of the left duct of Cuvier as it becomes the coronary sinus, it is easy to see why anomalies in the formation of the coronary sinus and the pulmonary veins at this point are possible. It is difficult to see why they are not more common, and it is probable that, with careful search of this area, more examples of pulmonary veins emptying into the coronary sinus will be found (Roberts). If the left anterior or cephalic cardinal vein persists as a permanent channel (as it occasionally does), there is a large left atrial posterior vein going obliquely across the back of the left atrium, known as the *vein of Marshall*, which is contained in a prominent fold of pericardium. When the vein atrophies, it becomes a fibrous cord in this pericardial fold known as the *ligament of Marshall*. This anomaly may result in a persistent left superior vena cava, opening into the end of the coronary sinus, or possibly into the left atrium. A much rarer anomaly is the persistence of the left inferior vena cava, opening into the lower part of the left end of the coronary sinus, or one of its tributaries, because of persistence of the left posterior or caudal cardinal vein (Figs. 1-53, 1-54).

The *3d phase* of development of the coronary arteries begins during the seventh week, when they first appear in embryos about 14 to 15 mm in crown-rump length. At this time, the coronary vessels are small channels with a

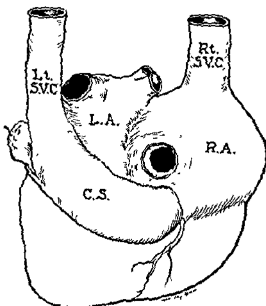


Fig. 1-53 Variations in the coronary sinus. Diagrammatic representation of heart from behind. Persistent left superior vena cava, Lt. S.V.C., joins the left extremity of the dilated coronary sinus, C.S., and the blood is carried into the right atrium, R.A. L.A., left atrium; Rt. S.V.C., right superior vena cava. (From Burchell, 1948.)

delicate endothelial lining, arising from the right anterior and from the left anterior part of the aorta; this occurs shortly after the aorta has been partitioned off in the division of the truncus arteriosus by longitudinal intrabulbar ridges, as these are hollowed out to contribute to the formation of the valve cusps of the aorta and pulmonary artery. The right and left coronary arteries may arise approximately at the same time, but the left (especially as studied in the pig embryo by Goldsmith and Butler, 1937) seems to branch earlier into its anterior descending and left circumflex branches These two branches, as well as the right coronary artery, extend by endothelial budding into the anterior interventricular sulcus and into the left and right AV sulci to reach their permanent position. The smaller branches of the coronary arteries break up into the very rich bed of smaller penetrating vessels and capillaries found throughout the myocardium, as previously described. Some of them make connection with the endothelium-lined spaces, sinusoids, and intertrabecular spaces, as the spongy myocardium atrophies, forming the arterioluminal channels.

Next follows the *4th phase*, which is the penetration of the myocardium by the terminal budding branches of the coronary arteries and veins so as to communicate with the capillaries

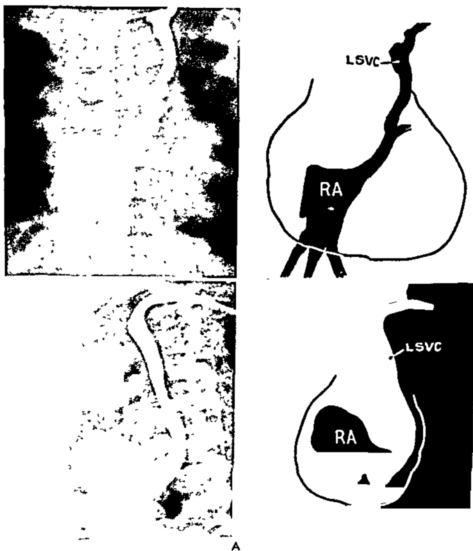


Fig. 1-54. A. Persistent left superior vena cava emptying into coronary sinus and right atrium in a 26-month-old girl. Frontal (upper right and left) and lateral (lower right and left) views at ½ sec after injection demonstrate the paramediastinal position of the persistent left superior vena cava (LSVC), which enters the right atrium posteriorly at the coronary sinus This anomaly is of no functional significance. (From Abrams and Kaplan. *Angiocardiographic Interpretation in Congenital Heart Disease*. Thomas, 1956. Courtesy of authors and publisher.)

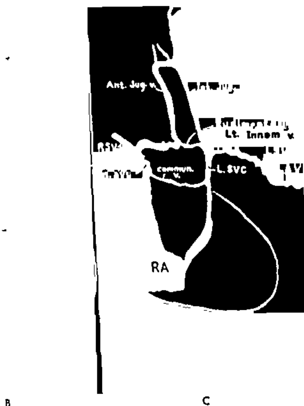


Fig 1-54 (Cont). B Massive systemic drainage to coronary sinus Absence of the inferior vena cava, associated with transposition of the viscera and levocardia Injection into the left brachial vein is followed by opacification of the left superior vena cava, *LSVC*, which empties into the right atrium at the coronary sinus ½ sec after injection. Note that the liver is on the left and the stomach on the right, but the grossly enlarged heart is in the normal position Injection into the left saphenous vein demonstrates a large venous trunk, collecting tributaries from the lumbar vertebral plexus, and joining the left superior vena cava at about the level where the azygos vein, *Az*, usually enters the right superior vena cava. Note the dense opacification of the paraspinal and vertebral veins In the LAO projection at 1 sec, the anomalous venous trunk is again shown, and almost certainly represents a hemiazygos vein Following right atrial filling there is an immediate shunt of opaque material into the left atrium through an atrial septal defect. This patient was thought to have an atrioventricularis communis with both atrial and ventricular septal defects C Drainage into coronary sinus from left superior vena cava in a 7-month-old boy Frontal projection at 1 sec. The opaque material, injected into the left antecubital vein, fills the axillary and subclavian veins, and demonstrates well both the left (*L SVC*) and the right superior vena cava (*R.SVC*) The left superior vena cava runs parallel to the right superior vena cava for most of its course and then dips posteriorly to enter the right atrium, *RA*, at the coronary sinus The force of the injection has allowed a moderate amount of reflux into the left internal jugular vein, *Int. Jug v.* The left innominate vein is small in this case, and most of the opacification of the right superior vena cava occurs by reflux into the internal jugular vein, and thence down through the anterior jugular vein. Note the small communicating vein, *commun v.*, between the two venae cavae. (From Abrams and Kaplan, *Angiocardiographic Interpretation in Congenital Heart Disease*. Thomas, 1956.)

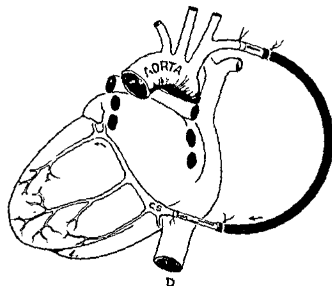


Fig. 1-54 (Cont.). D. Arterialization of the coronary sinus by a connection to the aortic branch as introduced by Joseph T. Roberts, 1938 (*Med. Ann. Dist. Columbia*, 1945)

and sinusoids of the intertrabecular spaces in the spongy myocardium.

The *5th phase* is the constriction of most of the intertrabecular spaces into capillaries and small sinusoids, with a few arteriolar and venular channels communicating with the coronary arteries and veins This results in the presence of the accessory coronary vascular system referred to previously as the "thebesian system," or the arteriovenoluminal, arteriocapillary luminal, arteriosinusoidal luminal, and venoluminal channels. Since these channels are the result of such a complicated embryogenesis, it is not surprising that their number, distribution, and size are variable in the adult heart The endothelium of the thebesian vessels, at least in the inner portion, originates from the endocardium

Phase 6 in the embryology of the vessels of the heart deals with the *development of the lymphatic system* in the heart, about which very little is known By inference, these channels may develop somewhat as do other peripheral lymphatic vessels. After the formation of the primary lymphatic sacs and channels, by about the seventh week, extensions of the smaller channels from the primary sacs and channels take place by the growth of endothelial sprouts. These are at first solid and then, as they extend, become hollow to form lymphatic vessels.

As studied by E. R. and E. L. Clark on amphibian larvae, it is inferred that a similar process occurs in human embryos (Patten, 1946). As the smaller channels expand peripherally, the lymphatic sacs are being molded into more restricted channels by the ingrowth of strands of connective tissue. These break the larger spaces into smaller channels, with a series of small and delicate tributary channels continuous with the peripherally growing sprouts. Since the left jugular lymph sac in the human embryo of 30 mm of length (8 to 9 weeks of age) is closely related to the left common cardinal vein with its innominate, jugular, and subclavian tributaries, it is plausible to assume that the cardiac lymphatic channels arise from the lymphatic sac in this area in a way similar to the origin of the coronary veins from the tributaries of the left cardinal vein The lymphatic channels form as solid cords of primordial endothelial cells which become hollowed, as do the blood vascular capillaries, with separation, however, of their points of drainage into larger channels.

The *nerve supply of the heart*, poorly understood even in the adult heart, develops as primordial ganglion cell clusters of the vagus, and later of the sympathetic nervous system growing from the neural crest into the heart muscle as it is forming. By the seventh week, the main vagal branches to the developing cardiac plexus are recognizable as they grow along the aortic and pulmonary trunks toward the main mass of the heart. As this occurs after the heart has already begun to beat, many of the nerves become related closely with the coronary blood vessels. Since the left ventricle and interventricular septum (the principal site of coronary disease) are derived from the left part of the early cardiac tube, connected to the left spinal cord, the usual referral of heart pain to the left is to be expected

Much remains to be learned about these interrelationships, both in the embryo and in relation to cardiac pain of adult patients (Gould, 1953) Earlier studies on the development of the cardiac-coronary circulatory system (Lewis, 1904, Martin, 1894, Tandler, 1908), as well as studies on the nerve supply of this region in the embryo (Streeter, 1912, Shaner, 1930) leave much for future correlation.

7

The aortic arch and its branches[1]

BARRY J. ANSON

GENERAL FEATURES

The arch of the aorta usually begins at the level of the upper border of the second sternocostal articulation of the right side In the first part of its course, the arch runs upward and to the left of the trachea (Figs 1-55, 1-56). Next, the arch is directed backward on the left side of the trachea, and finally passes downward on the left side of the body of the fourth thoracic vertebra. At the lower border of the arch, it becomes continuous with the descending aorta In this way two curvatures are produced: a proximal one with the convexity upward, a distal one with its convexity facing forward and to the left

The arch of the aorta is covered anteriorly by the pleurae and anterior margins of the lungs, and by the remains of the thymus As the vessel runs dorsally, the left side of the aortic arch is in contact with the left lung and pleura. On the left side, four nerves are related to the arch the *left phrenic*, the *superior cardiac branches of the left vagus*, the *superior cardiac branch of the left sympathetic*, and the *trunk of the vagus nerve* itself As the vagus nerve crosses the arch, it gives off a *recurrent branch*, which, after hooking around the vessel, ascends on its right side (Fig 1-56). The highest left intercostal vein runs obliquely upward and forward on the left side of the aortic arch, between the phrenic and vagus nerves To the right of the arch are the deep part of the cardiac plexus, the left recurrent nerve, the esophagus, and the thoracic duct, the trachea is situated behind and to the right of the vessel (Fig. 1-56). Cranial to the arch are the innominate, left common carotid, and left subclavian arteries—or these and sometimes other branches, in cases of aberrant development (discussed below). Caudad to the arch are the bifurcation of the pulmonary artery, the left bronchus, the ligamentum arteriosum, the superficial part of the cardiac plexus, and the left recurrent nerve (Fig. 1-56). The branches of the arch are crossed, close to their origins, by the innominate vein (Fig. 1-55).

Between the origin of the left subclavian artery and the attachment of the ductus arteriosus (Fig 1-56, inset), the lumen of the fetal aorta is considerably narrowed, forming an *isthmus* Just distal to the ductus arteriosus, the aorta presents a fusiform dilatation, the *aortic spindle*—the point of continuity of the two segments being marked in the concavity of the arch by an indentation or angle These conditions persist, to varying degree, in aortas of adults.

Typically, the height to which the aorta rises in the thoracic cavity is approximately 2.5 cm below the upper border of the sternum, however, the arch may ascend to the top of the bone, or descend to a point 8 cm below it In cases in which the thoracic and abdominal viscera are transposed, the aorta arches over the root of the right lung (*right aortic arch*) instead of over that of the left, and passes down on the right side of the vertebral column The aorta occasionally divides into an ascending and a descending trunk, the former of which, directed vertically upward, subdivides in turn into three branches, for the supply of the head

[1] In essentially present form, the text and figures for this chapter appeared in an article by Liechty, Shields, and Anson (see Bibliography)

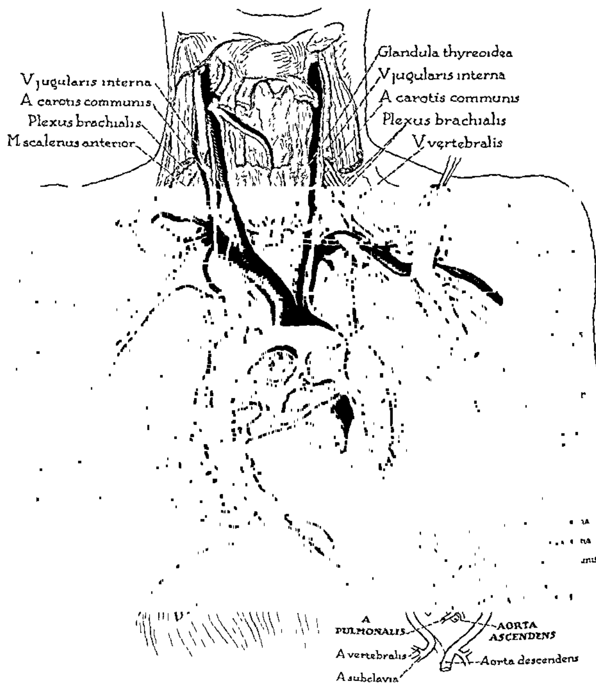


Fig. 1-55. *Ascending aorta, aortic arch, the regular arterial derivatives of the arch, and their branches in the neck. In the thorax the dissection demonstrates the contents of the middle and superior divisions of the mediastinum; in the neck the dissection has been carried to the level of the pharynx and larynx and the vascular structures of the carotid sheath. In the thorax the pericardial sac has been opened, the lungs have been cut near the hilum of each By excising the heart, the beginning of ascending aorta (transected) is shown, together with pulmonary and caval vessels where they leave or enter the heart. Between the aorta and the pulmonary artery, just deep to the pericardium (at *), is situated the ligamentum arteriosum. An arrow passes along the posterior wall of the transverse sinus. Inset, Transformation of the aortic arches in the human embryo, showing, schematically, the functional derivatives and the ductus arteriosus (From Greig et al., 1954.)*

Fig 1-56. Aortic arch, branches of the arch, and their trunks of supply to the neck and to the upper extremity. In the thorax the dissection has been carried into the posterior mediastinum. *Inset,* The form, angular course, and attachments of the ligamentum arteriosum are shown by elevating the remaining segment of the aortic arch and by drawing the pulmonary artery downward. (*From* Greig *et al*, 1954)

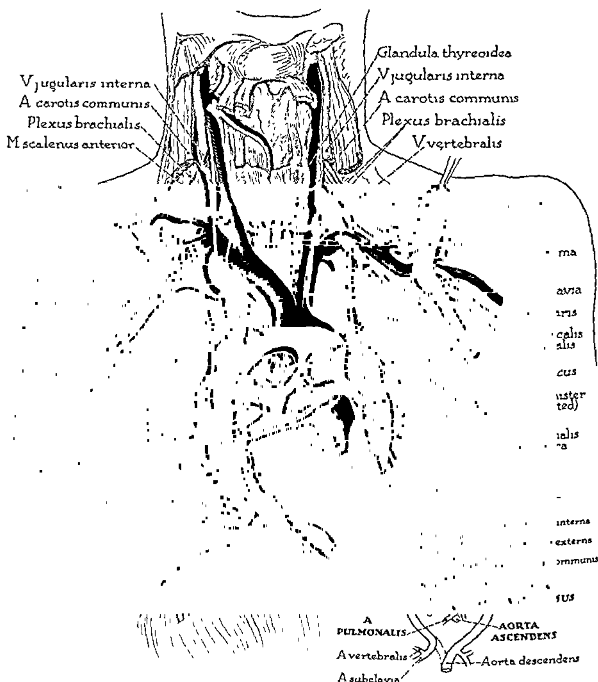


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ARCUS AORTAE

TYPES OF BRANCHING, 1000 SPECIMENS

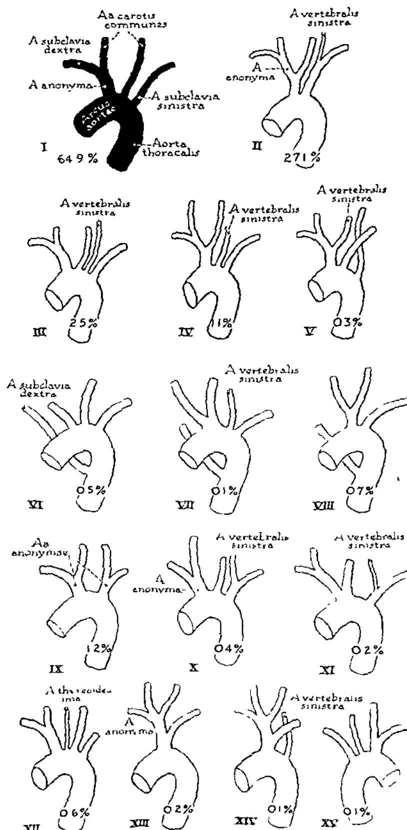


Fig. 1-57. Variations in branching of the aortic arch, types encountered in an examination of 1,000 specimens in the author's laboratory. I, The arrangement regarded as "normal" for man is actually encountered more frequently than all other types combined. Three branches leave the aortic arch, in the following succession from the specimen's right to left innominate (with right

and upper extremities. Sometimes the aorta subdivides near its origin into two branches, which soon reunite

In standard descriptions, the branches given off from the arch of the aorta are said to be, typically, three in number: the innominate, the left common carotid, and the left subclavian

VARIATIONS

Actually, the branches derived from the arch, instead of arising from the highest part of the arch, may spring from the commencement of the arch or upper part of the ascending aorta; or the distance between them at their origins may be increased or diminished, the number of the primary branches may be reduced (to *one, or more* commonly, two); increased to four, five, or six (the common carotid artery being absent on one or both sides, sometimes with the origin of both vertebral arteries from the arch). When the aorta *arches over to the* right side, the three branches have a reverse arrangement In other cases, where the aorta takes the usual course, the two carotid arteries may be joined in a common trunk, *and the* subclavian arteries arise separately from the arch, *the right* subclavian branch generally arising from the left end In rare instances, other arteries spring from the arch of the aorta—*these* are the bronchial, the thyreoidea ima, the internal mammary, and the inferior thyroid.

In the course of examination of specimens in the author's laboratory, it became evident that the "standard" type of branching from the aortic arch not only existed in the preponderant number of cases (approximately in two of three), but also, when placed with a rather ordinary variation thereof, gave a combined total which represented over 90 per cent of cases in a series of 1,000 specimens.

In comparison with the profound variations presented by Poynter (1916), the departures from the anatomic norm encountered in the author's series seem relatively undramatic Of course, in drawing from an extensive literature, Poynter gave the reader an imposing history of such arterial anomalies, including references from Vesalius (1543) to Valentin (1791), together with numerous reports in the nineteenth century, making a total of almost 1,100 references

As a third phase of the author's study, consideration was given to variations of surgical significance; here the number was further reduced

Of the 24 types pictured by Poynter, 7 are identical with those in the present author's *series* and are like those variations recorded as

common carotid and right subclavian derivatives); left common carotid, left subclavian II, An arrangement distinguished by reduction in the number of stems to two both [illegible] arising from the [illegible] in [illegible] is [illegible] replacement, the left vertebral artery (not the *left* common carotid artery, as in type I) being the second stem in right-to-left succession. Both common carotid arteries arise from *a common* stem (as in type II) V, In this variation the left vertebral artery arises from the innominate artery, and the order of the left common *carotid and* left subclavian arteries is reversed. VI to VIII, Three patterns similar in respect to the position of origin of the right subclavian artery, which, arising as the last branch of the arch, reaches the right upper extremity by passing dorsal to the esophagus In respect *to the origin* of the other branches, the types *differ*. IX, A bi-innominate sequence, in which paired vessels (in turn having matching main branches) are the only derivatives of the arch. X *and XI, In both these* varieties the left vertebral artery *arises* from an aortic trunk from which the left subclavian artery is also derived However, in type X a regular innominate artery is present (as in type I), whereas in type XI the "innominate" artery (with regular branches) *arises from an* aortic trunk shared with the left common carotid XII, Here, as in type III, an extra vessel arises from the arch between the innominate and the left subclavian, however, the added [illegible] vertebralis XIII [illegible] of branch [illegible] intermedi[illegible] [illegible] from a common stem (as in type XIII) with the excep[illegible] of the left vertebral, which arises from the arch to the *right* of the common stem XV, Reversal in direction of the arch in its course from heart to thoracic aorta; the branches maintain a normal succession in relation to the body itself, the position of the branches being a mirror image of the "standard" scheme of derivation. (*From Liechty, Shields,* and Anson, 1957)

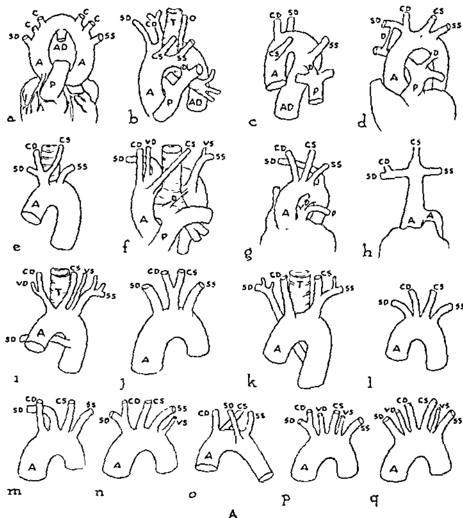


Fig. 1-58A. Arterial anomalies pertaining to the aortic arches and the branches derived therefrom. (Redrawn from Poynter) Abbreviations A, aorta, AD, aorta descendens; C, arteria carotis, CD, a. carotis communis dextra, CS, a carotis communis sinistra, D, ductus arteriosus; EC, a carotis externa, IC, a. carotis interna; O, esophagus, P, a. pulmonalis, SD, a subclavia dextra; SS, a. subclavia sinistra, T, trachea, VD, a. vertebralis dextra, VS, a vertebralis sinistra a, True double aortic arch, with three major trunks arising from each side of the arch (subclavian, internal carotid, and external carotid). The aorta descending arises at the confluence of the two arches. b, Division of the aortic arch, the two segments enveloping the trachea, the anterior division giving origin to the left common carotid and the left subclavian arteries and to a patent ductus arteriosus c, A right aortic arch from which the left common carotid artery arises as the first branch, the left subclavian artery as the last The latter artery shares a common short trunk with a patent ductus arteriosus. d, An aortic arch with persistent right and left arterial ducts, the former terminating in the right subclavian artery and the latter in the descending aorta e, An arrangement in which the left common carotid artery takes origin from the innominate trunk instead of from the aorta. f, Right aortic arch with the branches arising in the following order right common carotid, right vertebral, common trunk for the left common carotid and the right subclavian, and the left subclavian (the last-named branch providing origin for the left vertebral artery and receiving a patent ductus arteriosus). g, An arch in which the right subclavian artery arises as the last branch in the succession. An atretic pulmonary artery, leaving the heart as a fibrous cord, rapidly enlarges to normal caliber and is supplied by a patent ductus arteriosus h, A single branch arises from the aortic arch, all other branches taking origin from it directly or indirectly i, A right subclavian artery, of low origin, crosses posterior to the ascending aorta; the right vertebral arises from the right common carotid artery, the left vertebral from the aortic arch j, An arch which gives rise to a single trunk for both common carotid arteries and a subclavian artery on each side of the median stem k, Low origin of the right subclavian artery, the left common carotid and left subclavian arteries taking origin from a common stem l, Independent origin of each of the common carotid and subclavian arteries from the aortic arch. m, A configuration differing from the

surgically important in the pediatric literature (Liechty et al., 1957).

Author's Cases. In the specimens studied in the author's laboratory, only two types of variation are arresting, viz., that in which the right subclavian artery is the last branch of the aortic arch (Fig. 1-57, VI to VIII), and that (of entirely different embryologic origin) in which all regular branches arise from paired innominate arteries (Fig. 1-57, IX) or from a common stem (Fig. 1-57, XIII).

Collected Examples. In Poynter's monographic collection of irregular patterns of branching of the aortic arch (Fig. 1-58A, *a–q*), many schemes of derivation are presented which were not encountered in the author's series from 1,000 cadavers. They are described in the legend for Fig. 1-58A.

Clinical Selections. Some of the types of variation in the aortic arch and its branches, encountered as surgical problems, did not occur among the dissection room specimens. This is not unexpected, because these atypical patterns are likely to be associated with compression of the esophagus or trachea, or with the tetralogy of Fallot. The former condition, if left untreated, often results in an early death, caused by respiratory complications. Similarly, life expectancy in untreated cases of the latter sort is poor indeed.

Edwards (1948) has classified these anomalies on the basis of the source of the ductus arteriosus. In a study of 150 specimens (148 adults and 2 infants), records were taken on the anatomic features of the ductus arteriosus and the ligamentum arteriosum (Greig et al., 1954). No instance of complete aortopulmonary communication was found. In a single specimen in the adult series, a minute opening of pinpoint size remained at the pulmonary extremity of the ligament. In each of the infants, the ductus, although open at both aortic and pulmonary ends, was occluded midlength for a distance of 1 mm.

Group I—In this category belong those cases in which the *arterial duct arises from the left pulmonary artery* (Fig. 1-58B, *a*, *b*, *c*, *e*, *g*, *i*).

Group II—The second group includes the cases in which the *ductus arteriosus arises from the pulmonary artery of the right side* (Fig. 1-58B, *d*, *f*, *h*, *j*). Each of these patterns is the mirror image of one in group I (in Fig. 1-58B, arranged in pairs, *c* and *d*, etc.).

The *functioning double aortic arch* may show considerable difference in caliber of its two portions. The right arch is often the larger (Fig. 1-58B, *a*); in some instances the left is so small as to become obliterated in some part of its course (Fig. 1-58B, *b*). Ekstrom and Sandblom (1951), in a review of 85 cases of doubling, found compression (by the vascular ring) of the trachea or the esophagus, or of both visceral tubes, in 47 of the total number.

A *vascular ring* is formed by a *right-sided arch* associated with a left subclavian artery which is derived from an *aortic diverticulum* with a left-sided ductus arteriosus (Fig. 1-58B, *c*). The mirror image of this pattern is rare (Fig. 1-58B, *d*). However, both conditions have been reported as causing tracheal or esophageal obstruction. A variant of the above-described anomaly is represented by those cases in which the subclavian artery originates from the innominate artery (Fig. 1-58B, *e*, *f*). Again a ring is formed in this type by the connection between the ductus arteriosus and the pulmonary artery.

As established by the examination of laboratory specimens, an *aberrant right subclavian artery* (Fig. 1-58B, *g*) occurs with relative frequency among anomalies affecting the aortic arch. This anomalous condition often occurs in individuals with the tetralogy of Fallot—as does a variant of this vascular pattern, viz., one in which the arrangement is its mirror image. Bahnson and Blalock (1950) reported 36 such cases in a total of 841. The examples were equally divided between aberrant right (Fig. 1-58B, g) and aberrant left (Fig. 1-58B, *h*).

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preceding in that the right subclavian arises as the second branch of the aortic arch. *n*, An arch similar to the "standard," except for the addition of a left vertebral which arises as the last branch. *o*, A case in which the right subclavian arises as the third branch of the arch, not (as is commonly the case) from an innominate artery. *p*, An aortic arch with five branches, the vertebral arteries arising as the second and fourth members in the sequence. *q*, An arch with six branches, the subclavian, common carotid, and vertebral artery of each side being an independent aortic branch.

This anomaly gives rise to the condition known as *dysphagia lusoria*. It is of additional importance that the right laryngeal nerve is not recurrent; with no vessel arising in such a manner as to draw the nerve downward in looping course, the nerve of the right side (destined for the larynx) passes directly to its area of supply. In thyroidectomy or in tracheostomy, the unusual (and, therefore, unexpected) position of the nerve constitutes a surgical hazard.

Even in those cases in which the succession of branches of the aortic arch is "normal" (Fig. 1-58B, *i*), position of origin of the innominate artery may assume surgical significance, tracheal pressure may be the result of origin of the artery farther to the left on the aortic arch or, comparably, by the left common carotid when the latter vessel arises farther to the right than it does in normal cases (Gross, 1955).

The *right-sided aortic arch* with a system of branching which is the *mirror image* of the typical pattern (Fig. 1-58B, *j*) was encountered in 0.1 per cent of individuals, with the tetralogy of Fallot in 20 per cent, as reported by Blalock (1948). Self-evident is the importance of this arterial departure from the anatomic norm in selecting a site for thoracotomy in the Blalock-Taussig operation.

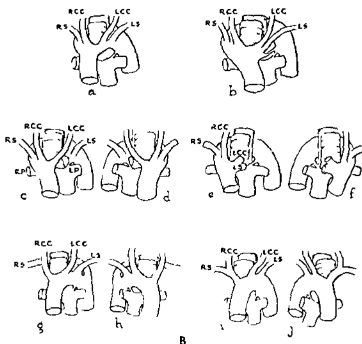


Fig. 1-58B. Clinically important anomalies of the aortic arch and its branches (Redrawn from Edwards, 1948.) The figures arranged in pairs are mirror images of each other. Abbreviations are as follows: LCC, left common carotid artery, LP, left pulmonary; LS, left subclavian; RCC, right common carotid; RP, right pulmonary, RS, right subclavian (From Liechty, Shields, and Anson, 1957.)

8

The abdominal aorta and its branches

NICHOLAS MICHELS

The abdominal aorta is a direct continuation of the thoracic aorta It enters the abdomen behind the diaphragm through the *aortic hiatus*, a triangular space situated at the level of the twelfth thoracic vertebra and formed by the middle arcuate ligament that arches across the midline connecting the two crura. In its descent, the abdominal aorta, which begins in the midline, deviates slightly to the *left* and terminates, in most instances, at the level of the lower third of the fourth lumbar vertebra by dividing into the two common iliac arteries and giving off the middle sacral artery The average length of the abdominal aorta, i e, the interval between the celiac and the division point of the aorta, is 13 74 cm for the male, 11 96 cm for the female (Taniguchi, 1931)

Since the abdominal aorta is *frequently* injected for roentgenologic delineation of its branches, its exact course and termination, and the vertebral levels of origin of its visceral branches, should be known

Adachi, in 208 bodies, found the termination point of the aorta to be at (1) the lower third of L4 (64 *bodies*); (2) the middle of L4 (50), (3) the disk between L4 and L5 (46), (4) the upper part of L5 (25), (5) the disk between L3 and L4 (3); (6) the lower L5 (2) Anson and McVay (1938) found the bifurcation point of the aorta to be situated between the middle third of L4 and the upper third of L5 in 84 per cent of 100 specimens The most common vertebral levels of origin of the visceral aortic branches encountered were celiac, L1 (74 per cent), superior mesenteric from middle of L1 to upper third of L2 (83 per cent); inferior *mesenteric* from middle of L3 to disk between L3 and L4, internal spermatic (ovarian) from lower third of L2 to upper third of L3 (64 per cent). Other extensive statistical analyses of the vertebral levels of the great vessels of the abdominal aorta are those of Broman (1908); Ssoson-Jaroschewitsch (1926), Heidsieck (1928); and Taniguchi (1931).

For arteriographic visualization with a radiopaque medium, first introduced by Dos Santos (1929), the classic site for aortic *puncture is* at the level of T12; for the celiac artery and its branches, T12, for the renal artery, at L1; and for the lower aorta and iliac arteries, L2 or L3 (Wagner et al, 1947). For further data on translumbar aortography, see Nelson, 1945; and Doss, 1946

The varied length of the abdominal aorta is determined by the extent to which fusion of the two primitive aortas occurred in the embryo For a description of this topic and the mode of origin of the definitive aortic branches (especially the gut arteries), the reader is referred to the author's atlas (Michels, 1955)

Branches of the abdominal aorta in the adult are the *parietal*, *visceral*, and *terminal*. They may be classified as follows.

- Visceral.
  - Paired·
    - *Suprarenals:*
      - Superior (multiple, from inferior phrenic)
      - Middle (from aorta)
      - Inferior (from renal)
    - Renal and renal polars
    - Internal spermatic or ovarian
    - Ureteric (2 or more)
  - Unpaired
    - Celiac
    - Superior mesenteric
    - Inferior mesenteric
    - (Aberrantly. common hepatic or right hepatic,

This anomaly gives rise to the condition known as *dysphagia lusoria*. It is of additional importance that the right laryngeal nerve is not recurrent; with no vessel arising in such a manner as to draw the nerve downward in looping course, the nerve of the right side (destined for the larynx) passes directly to its area of supply. In thyroidectomy or in tracheostomy, the unusual (and, therefore, unexpected) position of the nerve constitutes a surgical hazard

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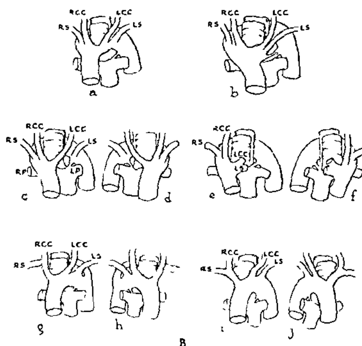


Fig. **1-58B** Clinically important anomalies of the aortic arch and its branches. (*Redrawn from Edwards,* 1948) The figures arranged in pairs are mirror images of each other Abbreviations are as follows *LCC*, left common carotid artery, *LP*, left pulmonary, *LS*, left subclavian, *RCC*, right common carotid; *RP*, right pulmonary, *RS*, right subclavian (*From Liechty, Shields, and Anson,* 1957.)

vertebral, (2) muscular, (3) a dorsal branch that supplies the spinal ramus, (4) fine twigs to extraperitoneal fat and the fat capsule of the kidney that anastomose with branches of the renal, phrenic, and colic arteries, constituting thereby the important subperitoneal plexus

Middle Sacral Artery. In most instances, it arises from the dorsal surface of the aorta, near its bifurcation point, i e, 2 to 16 mm from it. It supplies the fifth lumbar artery and, frequently, also the fourth As it enters the pelvis, it passes behind the hypogastric plexus and peritoneum Distally, it lies behind the rectum, where its rectal branches anastomose with the hemorrhoidal arteries Its parietal branches (lateral sacral) supply spinal twigs. An accessory middle sacral artery that courses anterior to the iliac vein occurs frequently (Poynter, 1923, Adachi, 1928).

VISCERAL BRANCHES OF THE AORTA

The Celiac Artery (Trunk, Axis). Typically, it arises from the aorta as the latter passes between the crura of the diaphragm at the aortic hiatus Its caliber varies considerably (8 to 40 mm in length, 7 to 20 mm in width). Its vertebral level is most commonly at the first lumbar vertebra, there are many variations, from the middle of T12 to the upper part of L2. The distance between the origin of the celiac and superior mesenteric arteries varies from 1 to 22 mm, most commonly being from 1 to 6 mm Occasionally, the two arteries arise contiguously or via a celiacomesenteric trunk

When typical and complete, the celiac artery gives off three branches, the hepatic, splenic (lienal), and left gastric, thus constituting a complete *hepatolienogastric trunk*, which furnishes practically the entire blood supply to the supracolonic organs (liver, gallbladder, stomach, duodenum, pancreas, and spleen) It is absolutely necessary to note, however, that this arrangement of the celiac trunk with its three branches occurs in only 55 per cent of the population (Michels, 1955) The celiac artery often lacks one or more of these branches It may be incomplete when the right, middle, or left hepatic artery arises from some other source, thereby constituting an incomplete hepatolienogastric trunk. Hence, in complete or incomplete form, such a trunk occurs approximately in 90 per cent of subjects, all other types of celiac trunks comprising the remaining 10 per cent. The celiac artery may omit the left gastric branch, forming a *hepatolienal trunk* (3 5 per cent), or the hepatic branch, forming a *lienogastric trunk* (5 5 per cent), or the splenic branch, forming a *hepatogastric trunk* (1.5 per cent).

Additive branches of the celiac artery comprise the dorsal pancreatic (22 per cent of subjects), the inferior phrenic arteries (74 per cent), and the middle colic or an accessory middle colic artery (1 5 per cent). Frequently, the celiac hepatic artery is absent, being replaced from the superior mesenteric artery, the aorta, or the left gastric artery. The tripod of Haller occurs in 25 per cent A tetrapod, formed by the addition of the dorsal pancreatic artery, occurs in 5 per cent

Other comprehensive investigations and statistical analyses of the celiac axis are those of Eaton, Lipshutz, Adachi, and Anson et al

Left Gastric Artery. In about 90 per cent of subjects, the left gastric artery arises from the celiac artery, most commonly as its first branch Varying in width from 2 to 8 mm, it is considerably larger than the right gastric artery, with which it anastomoses along the lesser curvature. Before its division into an anterior and posterior gastric branch, the left gastric artery supplies the cardioesophageal end of the stomach, either by a single ramus which subdivides, or by two to four rami given off in seriation by the main trunk Often, an accessory left gastric artery of splenic or celiac origin supplies the posterior surface of the stomach (*posterior gastric artery of Haller*). An accessory left gastric artery from the left hepatic artery to the anterior surface is less frequent.

The terminal branches of the left gastric artery anastomose with (1) branches of the right gastric artery; (2) short gastric arteries from the splenic terminal arteries or splenic superior polar or left gastroepiploic artery, (3) cardioesophageal branches from the left inferior phrenic artery (via its recurrent branch), the aberrant left hepatic artery (from the left gastric branch), the accessory left gastric artery (from the left hepatic branch), and from descending rami of the thoracic esophageal branches The degree of anastomoses about the cardioesophageal end of the stomach is variable. It may be extensive, or it may be sparse The latter fact is always to be remembered in regional gastroesophageal resections for, with-

dorsal pancreatic, transverse pancreatic, accessory middle colic)

Parietal:
 Paired:
  Inferior phrenic
  Lumbar (4 pairs)
  Common iliacs
  (Fifth lumbar)
 Unpaired:
  Middle sacral (originally a continuation of the aorta)
  Fifth lumbar, at times

Small branches of the abdominal aorta supply the vertebral column and contents of the vertebral canal (spinal cord) Information thereon may be found in texts of neuroanatomy.

PARIETAL BRANCHES OF THE ABDOMINAL AORTA

The Inferior Phrenic Arteries. Classical investigations on the inferior phrenic arteries and the role their collaterals play in the suprarenal blood supply are those of Levi (1909) and of Gérard (1911) Other comprehensive analyses of the phrenic arteries are those of Poynter (1923); Adachi (1928), Anson et al (1940–1951), Busch (1954), Michels (1955), and Merklin and Michels (1958).

The inferior phrenic arteries show a marked difference in site and mode of origin, a phenomenon correlated with the fact that, developmentally, they are branches of the adrenal arteries. Varying from 1 to 4 mm in caliber, they often are tortuous (at times, markedly so), similar to the testicular or ovarian arteries In 40 per cent of 200 subjects, the author found the inferior phrenic arteries arising by a common trunk that stemmed either from the aorta (20 per cent), the celiac artery (18 per cent), or the left gastric artery (2 per cent) An independent, bilateral origin of the phrenic artery occurred in 60 per cent and comprised the following types: both from the celiac artery or aorta, right from the aorta, left from the celiac artery or vice versa, right from the renal artery, or superior polar artery, left from the celiac artery or aorta

Infrequent aberrant origins of the phrenic arteries noted were from the renal or renal polar, internal spermatic or ovarian, left gastric, aberrant left hepatic (from left gastric), splenic, and aberrant right hepatic (from superior mesenteric) arteries. The cited percentages are comparable with those reported by Greig et al (1951). They distinguished 22 different patterns and noted a bilateral origin of the phrenic arteries in 66 per cent

After its origin, commonly between the crura, the inferior phrenic artery courses (right, under the inferior vena cava; left, under the esophagus) to the dome of the diaphragm, where it divides into a large anterior and small posterior branch. The latter anastomoses with the intercostal arteries, the former with the anterior branches of its fellow from the opposite side, with the musculophrenic branch of the internal mammary artery, and with the pericardiophrenic artery. Within the diaphragm, the phrenic arteries branch and, accordingly, communicate through the coronary ligament and bare area with the hepatic arterial system, thus constituting an important collateral pathway for the liver and for the pericardium.

Major branches of the inferior phrenic artery are (1) superior suprarenal arteries, which stem from the trunk, its posterior branch, or from both sources. *Multiple (5 to 20)* and usually threadlike in size, they supply the superomedial region of the suprarenal gland, commonly bifurcating just before entering the gland (2) *Recurrent* esophageal branch, given off by the left inferior phrenic artery after it has passed under the esophagus This branch is important, especially in a transthoracic esophagectomy, as *first performed* by Franz Torek (1913). *Its* ascending rami unite with the thoracic esophageal branches, its descending branches unite with the short gastric arteries of the splenic artery and with cardioesophageal branches of the left gastric artery or of a left hepatic artery derived from the left gastric artery. (3) Minute branches to the inferior vena cava, which may serve as a collateral route of blood supply to the liver.

Lumbar Arteries. Four pairs of lumbar arteries, corresponding to the lower thoracic intercostal arteries, arise opposite the bodies of the upper four lumbar vertebrae from the dorsal surface of the abdominal aorta, either separately or via a common trunk Since the aorta ends at L4, a fifth pair of lumbar arteries frequently arises from the middle sacral or internal iliac vertebra Proceeding forward in the lateral abdominal wall, they anastomose with the lower intercostal, iliolumbar, superior and inferior epigastric, and deep circumflex iliac arteries

Branches of the lumbar arteries are (1)

out the provision of an adequate regional blood supply, suture lines will not hold and there will be disconcerting postoperative effects—ischemia and necrosis, severe enough, at times, to be fatal (Shapiro and Robillard, 1950).

An important item, not sufficiently stressed, is the fact that in about 25 per cent of subjects, the left gastric artery gives off a large branch (2 to 4 mm wide, 5 cm long) to the left lobe of the liver This artery is either the *left hepatic artery itself*, being replaced from this source (12 per cent), or it is an *accessory left hepatic artery* (12 per cent) In either case, the artery from the left gastric artery enters the liver to supply either the entire left segment of the left lobe (when replaced) or the superior or inferior area of the lateral segment (when accessory). Severance of an aberrant left hepatic artery derived from the left gastric artery in gastric resections, leads to ischemia and subsequent fatal necrosis of the left lobe of the liver (seventh day, Hofmeister)

The Common Hepatic Artery. Typically, it arises from the celiac artery and, after giving off the gastroduodenal artery, becomes the hepatic artery proper, which divides into three branches, viz, the right, left, and middle hepatic arteries, the latter for the quadrate lobe Branches of the common hepatic artery are (1) right gastric artery, (2) gastroduodenal artery, (3) hepatic artery proper.

RIGHT GASTRIC ARTERY. It is invariably smaller (2 mm) than the left gastric artery (4 to 5 mm). In 200 bodies, it took origin from the common hepatic (40 per cent), left hepatic (40 5 per cent), right hepatic (5.5 per cent), middle hepatic (5 per cent), and gastroduodenal (8 per cent) arteries.

GASTRODUODENAL ARTERY. In most instances (75 per cent), it arises from the hepatic artery midway between the origin of the latter from the celiac artery and its division point. Because of its varied length (1 to 6 cm), terminal branching of the gastroduodenal artery may occur anywhere from the upper border of the duodenum, or above it, to the caudal border of the pylorus

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creas are an anterior and a posterior pancreaticoduodenal arcade made respectively by the superior pancreaticoduodenal, 18, and the *retroduodenal* (posterior superior pancreaticoduodenal) artery, 16 Both arcades join the superior mesenteric artery, 65, via a common inferior pancreaticoduodenal, 63. The artery of Wilkie, 15, to the first part of the duodenum has had a section of it removed The splenic artery, 38, is characteristically tortuous and distally gives off a superior polar artery, 40, to the spleen before dividing into its superior and inferior terminal branches

Near the juncture point of the splenic vein, 39, with the superior mesenteric vein, 65, is the *dorsal pancreatic artery*, 33. After supplying the neck region of the pancreas it gives off the *transverse pancreatic artery*, 35, which courses along the inferior surface of the pancreas, at the tail end of which it anastomoses with the a. pancreatic magna, 41, of the splenic and with the a caudae pancreatis, 46, from the left gastroepiploic, 47. To the right it anastomoses with the superior mesenteric, 65.

The anterior and posterior walls, 52, of the inferior recess, 55, of the omental bursa in the great omentum are shown Situated in the posterior wall of the great omentum below the transverse colon, 51, is the large *epiploic arc of Barkow*, 58, the left limb of which is made by the left epiploic, 54, from the left gastroepiploic, 47. The right limb is not shown but is made by the right epiploic from the right gastroepiploic, 13. Descending branches or anterior epiploic arteries, 72, from the infragastric arterial circle end in the arc, as do some of the descending branches or posterior epiploic arteries, 73, given off by the transverse pancreatic, 35, coursing in the pancreas The arc gives an additive blood supply to the transverse colon, 51.

The *retroduodenal artery*, 16, after its origin from the gastroduodenal, 14, swerves around the common bile duct, 17, supplying it and the ampulla of Vater in its course The retroduodenal arcade with its branches to the back of the duodenum, 26, here turned forward, is faintly visible behind the head of the pancreas

A portion of the body of the pancreas, 36, as well as a portion of its head, 71, have been cut away At the latter site is shown the union of the pancreatic duct, 19, with the common bile duct, 17. The major part of the stomach has been removed to show the retrogastric space of the omental bursa, 34, bounded dorsally by the pancreas The foramen of Winslow, 23, leads into the vestibule of the omental bursa, 24, where is visible the caudate lobe of the liver, 25 Relations of the portal vein, 12, to the hepatic arteries and bile ducts are shown, including the tributaries arising in the umbilical fossa, 1.



Fig. 1-59. Typical blood supply of the upper abdominal organs The various depths at which the structures and recesses actually lie and in which the arteries course are shown in proper perspective (Drawing by W B. McNett, a pupil of Brödel, using the author's pencil sketch as a guide. *From Morris' Human Anatomy, McGraw-Hill–Blakiston, 1953, and Michels' Blood Supply and Anatomy of the Upper Abdominal Organs, Lippincott, 1955*)

The celiac arterial pattern presented, i e, that of a celiac artery giving rise to the common hepatic, splenic and left gastric arteries, occurs only *in about one-half the population* (55 per cent), in the other half markedly different variations exist. Typically, the common hepatic artery divides into a right, *5*, left, *2*, and middle hepatic, *3*, the latter supplying the quadrate lobe or the medial segment of the left lobe, *6* The single cystic artery, *9*, arises in Calot's triangle and divides into its superficial branch, *8*, and the deep branch, *7*.

The cystic triangle of Calot, *11*, is formed by the angular union of the cystic duct, *10*, with the hepatic duct, *4*. The latter receives three ducts which, according to the plastic casts of Healey and Schroy, most probably represent a right duct for the anterior and posterior segment of the right lobe, a medial duct for the medial segment, and a lateral segment duct for the lateral segment of the left lobe.

The right hepatic artery, *5*, divides into its anterior and posterior segmental branch for the respective segments of the right lobe The left hepatic, *2*, divides into its superior and inferior area branch of the lateral segment of the left lobe The middle hepatic, *3*, supplies the medial segment of the left lobe. These statements are in accord with observations on the 150 vinyl plastic casts of human livers made by Healey and Schroy (the latter a graduate student under the supervision of the author) at the Daniel Baugh Institute of Anatomy.

The supragastric circle made by the right, 20, and left, 32, gastric and the infragastric circle made by the right, 13, and left, *47*, gastroepiploic arteries are shown. About the head of the pan-

out the provision of an adequate regional blood supply, suture lines will not hold and there will be disconcerting postoperative effects—ischemia and necrosis, severe enough, at times, to be fatal (Shapiro and Robillard, 1950)

An important item, not sufficiently stressed, is the fact that in about 25 per cent of subjects, the left gastric artery gives off a large branch (2 to 4 mm wide, 5 cm long) to the left lobe of the liver. This artery is either the *left hepatic artery itself*, being replaced from this source (12 per cent), or it is an *accessory left hepatic artery* (12 per cent). *In either case*, the artery from the left gastric artery enters the liver to supply either the entire left segment of the left lobe (when replaced) or the *superior or inferior area* of the lateral segment (when accessory) Severance of an aberrant left hepatic artery derived from the left gastric artery in gastric resections, leads to ischemia and subsequent fatal necrosis of the left lobe of the liver (seventh day, Hofmeister)

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The anterior and posterior walls, *52*, *of the* inferior recess, *55*, of the omental bursa in the great omentum *are shown* Situated in the posterior wall of *the great* omentum below the transverse colon, *51*, is *the large epiploic arc* of Barkow, *58*, *the left limb* of which is made by the left epiploic, *54*, from the left gastroepiploic, *47*. The right limb [illegible]
epiploic from [illegible]
from [illegible]
teric [illegible]
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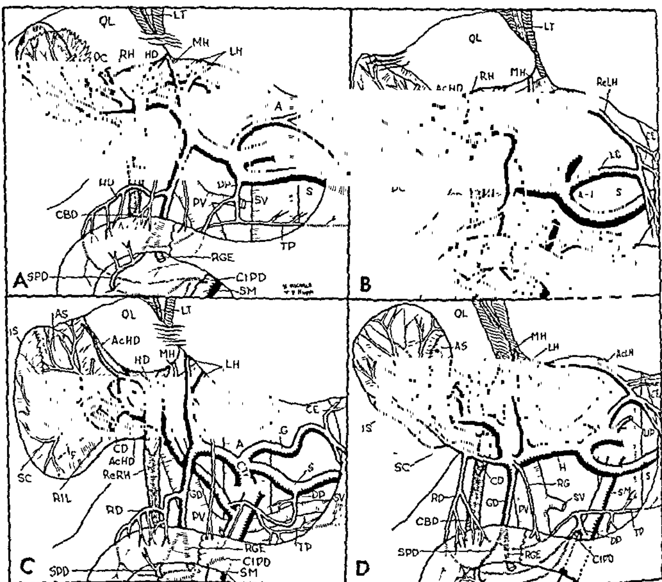


Fig. 1-60. A. Typical pattern The hepatic artery divides into a left, middle, and right branch, the middle supplying the quadrate lobe. Two cystic arteries, the superficial, SC, distributed to the peritoneal (free) surface, the deep, DC, to the nonperitoneal attached surface of the gallbladder and underlying liver substance. The cystic duct, CD, 6 cm, after a long, nearly parallel course with the hepatic duct, HD, swerves posterior to it to open into the common bile duct, CBD, just above the duodenum. The supraduodenal artery of Wilkie, SD, is distributed to the upper anterior and posterior surfaces of the first part of the duodenum The retroduodenal, RD (posterior superior pancreaticoduodenal), forms an extensive arcade on the posterior surface of the duodenum and head of the pancreas, then joins a posterior branch of the common inferior pancreaticoduodenal, CIPD. The dorsal pancreatic, DP, at junction of splenic vein with superior mesenteric is distributed to, and courses downward along, the dorsal surface of the neck of the pancreas; its prominent left branch, the transverse pancreatic, TP, runs along the inferior surface of the pancreas where it ultimately unites with a terminal branch of the splenic; its smaller right branch joins the superior pancreaticoduodenal, SPD; another branch supplies the uncinate process of the pancreas B. Type with a replaced left hepatic artery, ReLH, as the celiacal hepatic here gives origin only to the right, RH, and the middle hepatic, MH The artery supplying the left lobe of the liver is not an accessory hepatic, as commonly stated, but is the only left hepatic present being replaced by the left gastric, LG. The supraduodenal, SD, is a branch of the right hepatic, RH The dorsal pancreatic, DP, instead of coming from the celiacal trunk or one of its branches (first part of splenic or hepatic), arises from the superior mesenteric, SM The cystic artery, C, is double, for, as often is the case, its superficial and deep branch have separate origins. Interposed between them is a liver artery, RIL, most probably the posterior segmental branch of the right lobe, as judged from the liver casts of Healey and Schroy. Note the accessory hepatic duct, AcHD, near the deep cystic

Atypical origins of the gastroduodenal artery are from the left hepatic artery (11 per cent); right hepatic artery (7 per cent) middle hepatic artery (1 per cent); replaced hepatic trunk (3.5 per cent), celiac or superior mesenteric artery (2.5 per cent).

These atypical origins are correlated with the *mode* of branching of the celiac artery, for the common *hepatic artery may divide only into the gastroduodenal and right hepatic arteries, leaving the left hepatic artery to be replaced from the left gastric artery, or into the gastroduodenal and left hepatic arteries with replacement of the right hepatic from the superior mesenteric artery.*

Typical branches of the gastroduodenal artery comprise the retroduodenal, superior pancreaticoduodenal, and right gastroepiploic. Additive branches may be the supraduodenal, cystic or its superficial (anterior) branch, transverse pancreatic, and, occasionally, the middle colic.

RETRODUODENAL ARTERY (posterior superior pancreaticoduodenal). This important, little known artery (1 to 3 mm) constitutes the first collateral branch of the gastroduodenal artery. Its origin is often cryptic, i.e., hidden behind the first part of the duodenum and the head of the pancreas It comes in relation with the common bile duct twice, viz., at its origin, where it crosses the duct anteriorly from left to right, and at its end, where at about the middle of the posterior surface of the head of the pancreas, it crosses the duct posteriorly and anastomoses with a separate or common inferior pancreaticoduodenal artery from the superior mesenteric artery to form the posterior pancreaticoduodenal arcade, branches of which supply the common duct, all parts of the duodenum, and, to a less extent, the head of the pancreas The term *retroduodenal* (adopted by the author) is appropriate, the artery frequently (10 per cent) arises elsewhere than from the gastroduodenal artery, viz, from the hepatic, right hepatic, right gastric, or dorsal pancreatic arteries, as illustrated by the author in his descriptive atlas (see Bibliography). Severance of the retroduodenal artery in surgical procedures is very apt to cause *progressive necrosis* of the common bile duct, it being its main blood supply (Appleby, 1958).

SUPERIOR PANCREATICODUODENAL ARTERY. This is the smaller of the two end branches of the gastroduodenal artery and is frequently double After making a loop on the anterior surface of the head of the *pancreas, it sinks* into it, ascends, and joins the superior mesenteric artery via a separate or common inferior pancreaticoduodenal artery It forms the anterior pancreaticoduodenal arcade, supplying branches to all parts of the duodenum and giving off many pancreatic branches. Thus, the head of the pancreas and the loop of duodenum associated with it are supplied by branches (*vasa recta*) from *two pancreaticoduodenal arcades*, one anterior (formed by the superior

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artery, DC. C Type with a replaced right hepatic, *ReRH*, as the celiac hepatic gives rise only *to the gastroduodenal and left hepatic*. The right and quadrate lobes of the liver are supplied by a branch from the superior mesenteric, *SM This branch* is not, as commonly stated, an *accessory right hepatic*, but is a *replaced right hepatic*, ReRH. The cystic artery, C, here lies high; below it are the posterior segmental branch of the right lobe, *RlL*, entering the fissured area under the gallbladder, and a large (4-mm) accessory *hepatic duct*, *AcHD*, which runs close to and parallel with *the cystic duct*, *CD*. Emerging from the gallbladder bed is another accessory hepatic duct, AcHD, known as *the subvesical duct*, which may readily be torn in a cholecystectomy when filamentous, as is often the *case D Type with* an accessory left, AcLH The celiac hepatic gives off its characteristic three branches, right, middle, and left. Since the celiacal left hepatic *is small, there is an accessory* left hepatic, AcLH, from the left gastric, it being [illegible] *plies a definite secti*[illegible]

to 20 *per cent). T*[illegible]

right hepatic abov[illegible]

[illegible] the hepatic duct The superficial cystic, SC, arises from the *gastroduodenal* via its *retroduodenal*, RD, branch to the left of the hepatic duct, HD, and courses *caudad to the cystic duct, CD*. Note in particular how the blood supply of the posterior surface of the duodenum via the retroduodenal artery, RD, may be tied up *with that of* the gallbladder The cystic duct, CD, swerves to the posterior surface of the hepatic duct, HD, with which it is intimately *united* with connective tissue The *dorsal pancreatic*, *DP*, arises from the superior mesenteric, *SM*, and *has the common inferior* [illegible]

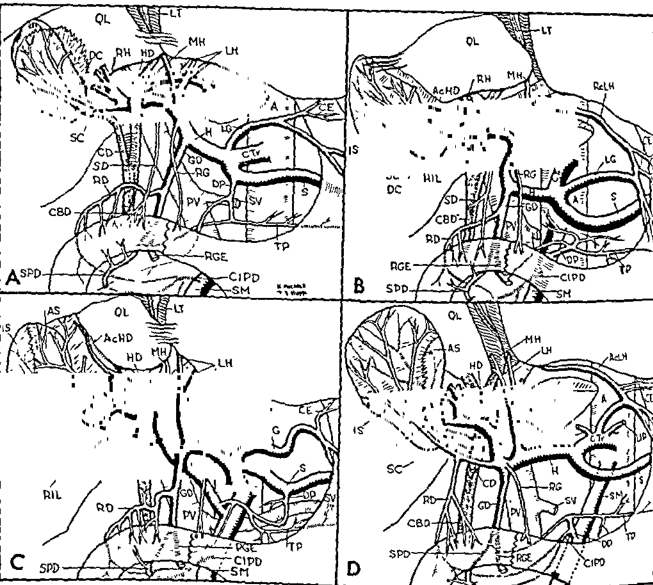


Fig. 1-60. A *Typical pattern* The hepatic artery divides into a left, middle, and right branch, the middle supplying the quadrate lobe Two cystic arteries, the superficial, *SC*, distributed to the peritoneal (free) surface, the deep, *DC*, to the nonperitoneal attached surface of the gallbladder and underlying *liver substance.* The cystic duct, *CD*, 6 cm, after a long, nearly parallel course with the hepatic duct, *HD*, swerves posterior to it to open into the common bile duct, *CBD*, just above the duodenum. The supraduodenal artery of Wilkie, *SD*, is distributed to the upper anterior and posterior surfaces of the first part of the duodenum The *retroduodenal*, *RD* (posterior superior pancreaticoduodenal), *forms* an *extensive* arcade on the posterior surface of the duodenum and head of the pancreas, then joins a posterior branch of the common *inferior pancreaticoduodenal*, *CIPD*. The *dorsal* pancreatic, *DP*, at junction of splenic vein with superior mesenteric is distributed to, and courses *downward* along, the *dorsal* surface of the neck of the pancreas; its prominent left branch, the transverse pancreatic, *TP*, runs along the inferior surface of the pancreas where it ultimately unites with a terminal branch of the splenic; its smaller right branch joins the superior pancreaticoduodenal, *SPD*; another branch supplies the uncinate process of the *pancreas.* B Type with a replaced left hepatic artery, *ReLH*, as the celiacal hepatic here gives origin only to the right, *RH*, and the middle hepatic, *MH* The artery supplying the left lobe of *the liver is not an accessory hepatic*, as commonly stated, but is the only left hepatic present being replaced by the left gastric, *LG*. The *supraduodenal*, *SD*, is a branch of the right hepatic, *RH* The *dorsal* pancreatic, *DP*, instead of coming from the celiacal trunk *or one* of its branches (*first part of splenic* or hepatic), arises from the superior mesenteric, *SM* The cystic artery, C, is double, for, as often is the case, its superficial and deep branch have separate origins Interposed between them is a liver artery, *RIL*, most probably *the posterior segmental branch* of the right lobe, as judged from the liver casts of Healey and Schroy. Note the accessory hepatic duct, *AcHD*, near the deep cystic

pancreaticoduodenal), the other posterior (formed by the retroduodenal artery). The arcades end in the superior mesenteric artery, either separately or via a common inferior pancreaticoduodenal artery The arcs may be double, triple, complete, or incomplete. Frequently, the inferior pancreat.coduodenal artery supplies jejunal branches or *arises from the upper jejunal arteries,* a point to be remembered in resections of this region It should be emphasized that the duodenal rami (vasa recta) from the pancreaticoduodenal arcades are *end arteries,* for when they are evulsed or ligated in gastrectomy, the *duodenal stump becomes devascularized, with resultant ischemic necrosis* (Shapiro and Robillard, 1946). *Severest effect* (7 to 10 days after operation) is a sudden fatal duodenal "blow out," suture lines not holding because of the lack of an adequate blood supply Likewise hazardous surgically *is the frequent condition* in which the inferior pancreaticoduodenal artery of the anterior or posterior arcade, or of both, instead of joining the superior mesenteric artery courses upward behind or *through the head of the pancreas to join an aberrant right hepatic artery* derived from the superior mesenteric artery

RIGHT GASTROEPIPLOIC ARTERY After giving off a large pyloric branch, it extends far beyond the midline of the lower border of the stomach, where it anastomoses with the left gastroepiploic artery *In 10 per cent of subjects, however, such anastomosis is absent or meager.* From the subgastric omental arc formed by the right and left gastroepiploic arteries, are given off *ascending* gastric arteries and descending omental or anterior epiploic branches The omental branches, short and long, descend between the two anterior layers of the great omentum The short branches unite with neighboring branches, the long ones proceed to the distal free edge of the great omentum, where they turn upward to become the posterior epiploic arteries Many of these branches join the large epiploic *arc of Barkow*, situated in the posterior layer of the great omentum, below the transverse colon The arc is usually formed by the *right epiploic artery* from the right gastroepiploic artery, and the *left epiploic artery* from the left gastroepiploic artery. From the arc ascend slender arteries that anastomose with similar branches (*posterior epiploic arteries*) given off from the middle and left colic arteries and from the transverse pancreatic artery, coursing along the inferior surface of the pancreas The ultimate and penultimate branches of the posterior epiploic arteries anastomose with the vasa recta of the middle colic artery but, apparently, are not of sufficient caliber to take over the blood supply, once the middle colic artery has been rendered functionless.

Aberrancies of the right gastroepiploic artery comprise (1) origin from the superior mesenteric artery (1 5 per cent), or with the middle colic and superior pancreaticoduodenal arteries (1 per cent); (2) anastomosis with the middle colic artery via a large vessel (1 per cent); (3) origin from a gastroduodenal artery derived from the superior mesenteric artery (two cases); (4) origin from the superior mesenteric artery via a common inferior pancreaticoduodenal artery (*one case*). An additive branch of the gastroduodenal artery frequently encountered is *the supraduodenal artery,* distributed to the first inch of the duodenum. *It often takes* origin from the gastroduodenal artery (25 per cent) or from its retroduodenal branch (50 per *cent)* Other sites of its origin are the hepatic artery (5 per cent), right hepatic artery (5 per cent), left and middle hepatic arteries (1.5 per

large liver artery (most *probably* the posterior segmental branch of the right hepatic [illegible]
latter enters the fissured area under the [illegible]
the [illegible]
[illegible] superior mesenteric via
[illegible] B Hepatic trunk from *the left* gastric—surgically a dan-
gerous case in partial *and in total* gastrectomy Here the entire blood supply of the liver and
gallbladder comes from the left side, i e , from the left gastric via *a replaced* hepatic trunk which
runs at the periphery of the lesser omentum and when the abdomen is opened, is largely hidden
from view. The cystic arises from the middle hepatic, *MH*, and after crossing the hepatic duct
divides into its superficial, SC, and deep branch, DC Surgically, it is important to know that the
middle colic, *M Col*, may arise from the celiac and give origin to the dorsal pancreatic, as here.
Branches of the left inferior phrenic supply the esophagus

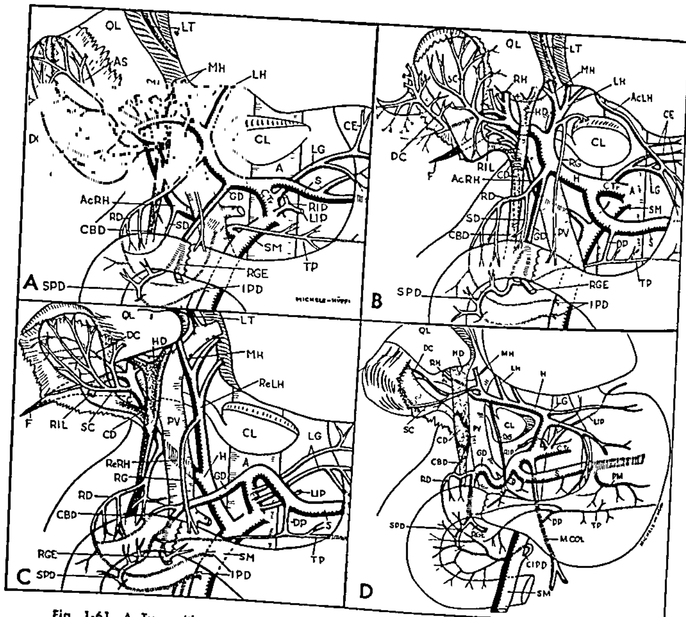


Fig. 1-61. A. Type with an accessory right hepatic artery, *AcRH*, as the hepatic divides into left, middle, and right branches Since the celiacal right hepatic gives off only the cystic, *C*, and a very small liver branch, an accessory right hepatic, *AcRH*, from the superior mesenteric supplies the right lobe; before doing so it anastomoses with the right hepatic. The retroduodenal, *RD*, is a branch of the hepatic and not of the gastroduodenal, thereby justifying its own terminology. It descends anterior to the common bile duct, *CBD*, forms an extensive arcade on the posterior surface of the duodenum and head of the pancreas, then unites with the accessory right hepatic via its own inferior pancreaticoduodenal, *IPD*. The cystic duct, *CD*, joins the common hepatic duct anteriorly, and to the left it is dangerously close to the accessory right hepatic, *AcRH*. The latter gives off the supraduodenal, *SD*, which anastomoses with the retroduodenal Single cystic artery with typical distribution of its superficial and deep branch B. Type in which the liver has five major arteries, three from the celiacal hepatic and two accessory hepatic arteries (accessory right hepatic, *AcRH*, from the superior mesenteric, *SM*, and the accessory left hepatic, *AcLH*, from the left gastric, *LG*). The deep cystic, *DC*, after giving off a liver branch and supplying the attached surface of the gallbladder, ramifies in areas beyond it as a relatively large liver artery. The cystic duct, *CD*, is long (6 cm) and swerves posterior to the hepatic duct, with which it is intimately united with connective tissue for 7.5 cm before opening into the common bile duct, *CBD*. Note how the accessory right hepatic, *AcRH*, most likely the posterior segmental branch of the right lobe, enters the fissured area under the gallbladder and how readily it may be mistaken for the cystic. C. Type without a celiacal hepatic. The entire blood supply of the liver comes from the superior mesenteric, *SM*, via a replaced common hepatic, the right branch of which courses upward dorsad to the portal vein, *PV*. Note close relation of the cystic artery, *C*, to the

cent) The supraduodenal artery is not an end artery, as claimed by Wilkie (1911), but often is anastomosed with neighboring vessels, especially the right gastric artery. Other branches include (1) the cystic artery, or its superficial (anterior) branch, which in certain cases (4 per cent) takes origin from the gastroduodenal artery or its retroduodenal branch, (2) the transverse pancreatic artery, usually a branch of the dorsal pancreatic artery from the splenic artery, may take origin from it, thus establishing a long transpancreatic collateral pathway between the spleen and the liver

The Hepatic Artery Proper. Typically, the hepatic artery of celiac origin, as it approaches the porta hepatis, divides into three branches, viz, a *right hepatic* to supply the anterior and posterior segments of the right lobe of the liver, a *left hepatic* for the left segment of the left lobe, and a *middle hepatic* (branch of the right or left hepatic) to supply the quadrate lobe or medial segment of the left lobe.

RIGHT HEPATIC ARTERY. In most instances (85 per cent), it crosses the hepatic duct dorsally, purely ventral crossings have been observed in 12 per cent of 200 subjects. Often, the celiac right hepatic artery is represented by two branches, because of an early division of the right hepatic artery into its respective anterior and posterior segmental branches. Both branches may cross the hepatic duct dorsally or ventrally, or they may have the hepatic duct between them. In the *cystic triangle of Calot*, formed by the angular union of the cystic duct with the hepatic duct, the right hepatic artery is extremely variable in its course, which may be high, low, or intermediate Variable, likewise, are the sites at which it gives off the cystic artery, breaks up

tum, blood may be routed directly into the gastroduodenal, GD, through right gastroepiploic, RGE, and right epiploic, RE, in type 1, indirectly into it via posterior epiploic, PE, transverse pancreatic, TP, and its connections in type 2 Left limb of arc is always made by the left epiploic, LE. 4 *Paraesophageal—or hepatogastric.* Cardioesophageal, CE, branches from the left gastric, LG, and splenic, S, via its short gastrics, SG, unite with similar branches from accessory left hepatic, AclH. 5 Retroesophageal Recurrent branch of left inferior phrenic gives off cardioesophageal, CE, branches that unite with those *derived from* accessory left hepatic, AclH, short gastrics, SG, and accessory *left gastric*, AclG 6 Transpancreatic Blood leaving the splenic, S, through the dorsal pancreatic, *DP, or a. pancreatica* magna, *PM*, and caudal pancreatic, CP, or coming from the arc of Barkow through a posterior *epiploic, PE*, enters the transverse pancreatic, *TP*, via which it may course into the superior pancreaticoduodenal, *SPD*, right gastroepiploic, *RGE*, or gastroduodenal, GD, to reach the hepatic trunk, H III Routes over arteries outside the celiac blood supply 1. Superior mesenteric, *SM*, via *the inferior* pancreaticoduodenal and the anterior and posterior pancreaticoduodenal arcades, *respectively*, made by the retroduodenal, *RD*, and superior pancreaticoduodenal, *SPD*, branches of the gastroduodenal, *GD*. 2 Superior mesenteric via its transverse pancreatic, *TP*, branch, which may connect with the *SPD*, *RGE*, or GD 3 Inferior phrenics coursing in the diaphragm unite with branches of the hepatic at attached areas of liver. Cardioesophageal, CE, branches of the *recurrent* branch of the *left inferior* phrenic anastomose with subcapsular branches of the hepatic in fossa for ligamentum venosum 4. Superior phrenic from the terminal branches of the internal *mammary, i e*, superior epigastric and musculophrenic communicate with branches of hepatic in diaphragm. 5 Ensiform *branch of the* internal mammary (Haller, 1756) *coursing in the falciform* ligament and ligamentum teres unite with terminal falciform branches given off by the left, LH, and middle hepatic, *MH* 6 Vasa vasorum An arteriole derived from the right inferior phrenic courses upward *to liver along* inferior vena cava, *IVC*. 7. Supply *along the* biliary ducts by arteriole *derived f*...

The collateral pathways outlined ...
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ström have definitely *committed* themselves to the opinion *that some* of the so-called "liver deaths" ...nd, Gordon-Taylor, Vaughn, Gray, and Ram-
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mined only in further studies, such as animal experimentation, arteriograms, and post-mortem
investigations (*From Michels' Blood Supply and Anatomy of the Upper Abdominal Organs*,
Lippincott, 1955)

INTERNAL MAMMARY
XIPHOID
INTERNAL MAMMARY
ENSIFORM BRANCH
SUPERIOR EPIGASTRIC
FALCIFORM LIG.
AND
LIG. TERES
MUSCULOPHRENIC
LEFT SUPERIOR
ENT
ICH
OLAR
ND
AcLG

Fig. 1-62. Some of the 26 collateral arterial pathways to the liver, as ascertained in 200 dissections I Routes through hepatic arteries arising from sources other than the common celiac hepatic trunk 1. Accessory left hepatic, AcLH, from the left gastric, LG. 2. Accessory right hepatic, AcRH, from superior mesenteric, SM. II. Nonhepatic routes capable of connecting with branches of severed hepatic arteries. 1. Infragastric via right and left gastroepiploics, RGE> <LGE, and gastroduodenal, GD, to the right, and short gastrics, SG, to the left. 2. Supragastric, via right and left gastrics, RG> <LG. 3. Infracolic, via the arc of Barkow in posterior layer of the great omen-

cent). The supraduodenal artery is not an end artery, as claimed by Wilkie (1911), but often is anastomosed with neighboring vessels, especially the right gastric artery. Other branches include (1) the cystic artery, or its superficial (anterior) branch, which in certain cases (4 per cent) takes origin from the gastroduodenal artery or its retroduodenal branch, (2) the transverse pancreatic artery, usually a branch of the dorsal pancreatic artery from the splenic artery, may take origin from it, thus establishing a long transpancreatic collateral pathway between the spleen and the liver

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The collateral pathways outlined here on an anatomic basis, many of them small and insignificant, should *by no sort of deductive reasoning give rise to the impression that ligation of a major hepatic artery can be performed with impunity* Behrend, Gordon-Taylor, Vaughn, Gray, and Ramström have definitely committed themselves to the opinion that some of the so-called "liver deaths" following cholecystectomy are attributable to severance, ligation, or clamping of the right hepatic artery The actual efficiency of the outlined 26 collateral pathways to the liver can be determined only in further studies, such as animal experimentation, arteriograms, and post-mortem investigations (*From Michels' Blood Supply and Anatomy of the Upper Abdominal Organs*, Lippincott, 1955.)

into its segmental branches, and supplies its branch to the caudate lobe.

Inside and outside the cystic triangle, the right hepatic artery often makes *a characteristic caterpillar-like loop*, with convexity that points downward, upward, to the right, or to the left. In cholecystectomies, such sinuosities of the right hepatic artery are *extremely vulnerable*, for the cystic artery may arise from the distal or proximal end of the loop. In many instances (12 per cent), with two right hepatic arteries in the cystic triangle, one is derived from the celiac hepatic artery and is distributed to the anterior segment, the other is replaced from the superior mesenteric artery and supplies the posterior segment of the right lobe, which it enters through a fissured area below the gallbladder. The fissure is a lateral extension of the porta hepatis and may be the external surface marking of the beginning of the lateral segment fissure dividing the right lobe of the liver into an anterior and posterior segment. (Fig. 1-59).

CYSTIC ARTERY In 75 per cent of subjects it is a single vessel. Typically, it arises from the right hepatic artery in *Calot's triangle*. Upon approaching the gallbladder, it divides into a superficial (anterior) and deep (posterior) branch, the former distributed to the free peritoneal, the latter to the attached surface of the gallbladder. Both branches give off a variable number of liver twigs, which in certain cases are actually liver arteries of considerable size. *This standard description of the cystic artery is inadequate, for in every subject, the cystic artery is different and merits careful inspection by the surgeon*, lest the wrong artery (as the right hepatic) be severed with postoperative complications and often fatal necrosis of the right lobe of the liver (Keith, Flint, Moynihan, Gordon-Taylor, Walters, Lahey, Cattell, Ravdin, Cole, Behrend, Ramstrom, and many others).

Statistically (on the basis of 200 dissections), the cystic artery arises to the right of the hepatic duct from the right hepatic branch of the celiac artery only in 62 per cent of cases. In 18 per cent, it arises in the triangle from aberrant right hepatic arteries derived from the superior mesenteric artery or aorta. In 20 per cent of cases, *the cystic artery does not arise in the cystic triangle at all, but outside of it*, taking origin from various arteries, such as the right, common, left, or middle hepatic arteries or the gastroduodenal artery and its retroduodenal branch. In the latter two cases, the course of the cystic artery is often below the cystic duct, a fact to be remembered in every cholecystectomy.

DOUBLE CYSTIC ARTERIES In 25 per cent of subjects, the cystic artery is double, because its superficial and deep branches have separate origins—from the same right hepatic artery at different points, inside or outside, of the triangle, or from two different hepatic arteries (right, middle, left), or from a celiac hepatic artery and some other regional vessel, such as the gastroduodenal, retroduodenal, or replaced or accessory right hepatic artery from the superior mesenteric artery, incidence of the latter being 12 per cent. A common pattern of dual cystic arteries is the one in which the deep cystic artery (often hidden) arises from the right hepatic artery high in the triangle, and the superficial artery arises from the middle or left hepatic artery or from the gastroduodenal artery outside the triangle.

LEFT HEPATIC ARTERY. Typically, it is a branch of the celiac hepatic artery proper and distally terminates in two main branches for the respective superior and inferior areas of the lateral segment of the left lobe. Occasionally, one of the terminal branches supplies a ramus to the quadrate lobe.

In 12 per cent of subjects, the left hepatic artery arises from the left gastric artery and is then known as a *replaced left hepatic artery*. When two left hepatic arteries are present, one from the celiac, the other from the left gastric artery, the additional artery is a true *accessory left hepatic artery* (13 per cent), being the sole supply to the superior area of the lateral segment. Branches of the left hepatic artery comprise the right gastric artery, a caudate branch, and if derived from the left gastric artery, several cardioesophageal branches, and, occasionally, a large accessory left gastric or inferior phrenic artery.

MIDDLE HEPATIC ARTERY This artery, so named by Haller in 1756, is a constant artery supplying the quadrate lobe or medial segment of the liver. In about equal proportion (40 per cent of 200 cases), it arises as a branch of the right or left hepatic artery, in the remaining 20 per cent, it has a separate origin. In some instances, it is the only hepatic arterial component of celiac origin, both the right and left hepatic arteries being replaced from other sources. Reaching the umbilical fossa, it supplies branches to the quadrate lobe (medial segment) and often gives a branch or two to the lateral segment of the left lobe. Occasion-

ally, it gives rise to the cystic artery, usually its superficial branch

TERMINAL HEPATIC BRANCHES The three hepatic arteries, upon reaching the liver, subdivide, the right hepatic artery, into an anterior and posterior segmental branch; the left hepatic artery, into a superior and inferior area branch of the lateral segment of the left lobe; and the middle hepatic artery, into two superior and two inferior area branches for the medial segment of the left lobe This distribution of the hepatic arteries is based on a statistical analysis of intrahepatic arteries in 150 human livers made by Healey and Schroy (1952). All three hepatic arteries participate in the blood supply of the caudate lobe, a common pattern being a branch of the right hepatic artery for the caudate process and a branch from the left hepatic artery for the caudate lobe proper

In addition to their main branches, the three hepatic arteries, collectively, give off numerous (20 to 30) subcapsular twigs that ramify, especially in the fossa for the ligamentum venosum Extrahepatically, the main hepatic branches frequently anastomose, the most common variety being a union of the right and left hepatic branches at or near the porta hepatis Such anastomosis between hepatic branches does not, however, occur inside the liver, for here, *every hepatic artery is an end artery*, as demonstrable in vinyl acetate corrosion casts of the liver Branches of both the middle and left hepatic arteries in the umbilical fossa are prolonged into the falciform ligament, where they anastomose with descending rami of the internal mammary artery, thereby affording, via this collateral pathway, the possibility of a backflow of blood into the liver from the thoracic region.

Aberrant Hepatic Arteries. An aberrant hepatic artery arises from a source other than the celiac axis. Aberrant hepatic arteries comprise two types, viz., *replaced* and *accessory*, the former being substituted, the latter additive, vessels Replaced right hepatic arteries take origin predominantly from the superior mesenteric artery and, less often, from the aorta, gastroduodenal, retroduodenal, cystic, or dorsal pancreatic artery Replaced left hepatic arteries arise, nearly exclusively, from the left gastric artery. In some instances, (2.5 per cent), the entire hepatic trunk may be replaced by a vessel arising from the aorta, the superior mesenteric artery, and rarely, the left gastric artery. Accessory hepatic arteries take origin from various sources on the right side, predominantly from the superior mesenteric artery, and, on the left side, from the left gastric artery. Some sort of an aberrant hepatic artery, either replaced or accessory, occurs in approximately 42 per cent of subjects. Aberrant right hepatic arteries from the superior mesenteric artery frequently give rise to one or two cystic arteries, a fact of surgical import in the search for the cystic artery

In a statistical analysis of 200 bodies investigated by the author, 12 per cent had one aberrant hepatic artery, and 10 per cent had two or more. Of the aberrant right hepatic arteries encountered, 18 per cent were of the replaced type and 8 per cent accessory Of the aberrant left hepatic arteries, 15 5 per cent were replaced, 11 5 per cent were accessory About three-fourths of the aberrant right hepatic arteries from the superior mesenteric artery (17 per cent, including replaced hepatic trunks) constituted replaced hepatic arteries, i e., *the only right hepatic artery present*, while about one-half the aberrant hepatic arteries from the left gastric artery constituted replaced left hepatic arteries, i e , *the only left hepatic artery present.*

No hepatic artery, whether replaced or accessory, can be dispensed with, for, as shown by Healey and Schroy (1953), aberrant hepatic arteries supply definite liver regions the replaced variety, an entire lobe; the accessory variety, a section of one of the lobes *Severance of an aberrant right hepatic artery from the superior mesenteric artery during cholecystectomy, or of a left hepatic artery from the left gastric artery during a gastric resection,* produces [illegible]

[illegible] 1945).

Strikingly at variance with standard descriptions is the fact that the so-called normal type (a celiac hepatic artery with right and left branches) occurs in only 55 per cent of cases Despite the complexity and varied character of the remaining types of the hepatic arterial blood supply, any sample of it may, with minor modifications, be classified as one of the following basic types

The celiac hepatic artery supplies

1 The right, left, and middle hepatic arteries (standard type, 55 per cent, Fig 1-60A).

2. The right and middle hepatic arteries—the left

into its segmental branches, and supplies its branch to the caudate lobe.

Inside and outside the cystic triangle, the right hepatic artery often makes *a characteristic caterpillar-like loop,* with convexity that points downward, upward, to the right, or to the left. In cholecystectomies, such sinuosities of the right hepatic artery are *extremely vulnerable,* for the cystic artery may arise from the distal or proximal end of the loop. In many instances (12 per cent), with two right hepatic arteries in the cystic triangle, one is derived from the celiac hepatic artery and is distributed to the anterior segment, the other is replaced from the superior mesenteric artery and supplies the posterior segment of the right lobe, which it enters through a fissured area below the gallbladder. The fissure is a lateral extension of the porta hepatis and may be the external surface marking of the beginning of the lateral segment fissure dividing the right lobe of the liver into an anterior and posterior segment (Fig 1-59).

CYSTIC ARTERY. In 75 per cent of subjects it is a single vessel. Typically, it arises from the right hepatic artery in *Calot's triangle.* Upon approaching the gallbladder, it divides into a superficial (anterior) and deep (posterior) branch, the former distributed to the free peritoneal, the latter to the attached surface of the gallbladder Both branches give off a variable number of liver twigs, which in certain cases are actually liver arteries of considerable size *This standard description of the cystic artery is inadequate, for in every subject, the cystic artery is different and merits careful inspection by the surgeon,* lest the wrong artery (as the right hepatic) be severed with postoperative complications and often fatal necrosis of the right lobe of the liver (Keith, Flint, Moynihan, Gordon-Taylor, Walters, Lahey, Cattell, Ravdin, Cole, Behrend, Ramstrom, and many others).

Statistically (on the basis of 200 dissections), the cystic artery arises to the right of the hepatic duct from the right hepatic branch of the celiac artery only in 62 per cent of cases. In 18 per cent, it arises in the triangle from aberrant right hepatic arteries derived from the superior mesenteric artery or aorta. In 20 per cent of cases, *the cystic artery does not arise in the cystic triangle at all, but outside of it,* taking origin from various arteries, such as the right, common, left, or middle hepatic arteries or the gastroduodenal artery and its retroduodenal branch In the latter two cases, the course of the cystic artery is often below the cystic duct, a fact to be remembered in every cholecystectomy.

DOUBLE CYSTIC ARTERIES. In 25 per cent of subjects, the cystic artery is double, because its superficial and deep branches have separate origins—from the same right hepatic artery at different points, inside or outside, of the triangle, or from two different hepatic arteries (right, middle, left), or from a celiac hepatic artery and some other regional vessel, such as the gastroduodenal, retroduodenal, or replaced or accessory right hepatic artery from the superior mesenteric artery, incidence of the latter being 12 per cent A common pattern of dual cystic arteries is the one in which the deep cystic artery (often hidden) arises from the right hepatic artery high in the triangle, and the superficial artery arises from the middle or left hepatic artery or from the gastroduodenal artery outside the triangle.

LEFT HEPATIC ARTERY. Typically, it is a branch of the celiac hepatic artery proper and distally terminates in two main branches for the respective superior and inferior areas of the lateral segment of the left lobe. Occasionally, one of the terminal branches supplies a ramus to the quadrate lobe.

In 12 per cent of subjects, the left hepatic artery arises from the left gastric artery and is then known as a *replaced left hepatic artery.* When two left hepatic arteries are present, one from the celiac, the other from the left gastric artery, the additional artery is a true *accessory left hepatic artery* (13 per cent), being the sole supply to the superior area of the lateral segment. Branches of the left hepatic artery comprise the right gastric artery, a caudate branch, and if derived from the left gastric artery, several cardioesophageal branches, and, occasionally, a large accessory left gastric or inferior phrenic artery

MIDDLE HEPATIC ARTERY This artery, so named by Haller in 1756, is a constant artery supplying the quadrate lobe or medial segment of the liver In about equal proportion (40 per cent of 200 cases), it arises as a branch of the right or left hepatic artery; in the remaining 20 per cent, it has a separate origin In some instances, it is the only hepatic arterial component of celiac origin, both the right and left hepatic arteries being replaced from other sources Reaching the umbilical fossa, it supplies branches to the quadrate lobe (medial segment) and often gives a branch or two to the lateral segment of the left l[illegible]

ing in the tail of the pancreas, it swerves to the right to anastomose with the transverse pancreatic branch, which it assists in supplying blood to the pancreatic duct.

The *caudal pancreatic artery* is the last large branch of the splenic trunk, although it frequently arises from a terminal branch of the latter or from the left gastroepiploic artery. Entering the tail of the pancreas, it communicates with branches of the a. pancreatica magna and the transverse pancreatic artery

LEFT GASTROEPIPLOIC ARTERY. As a rule, it arises from the splenic trunk 1 to 3 cm proximal to its primary terminal division Frequently, it takes origin from the inferior terminal of the splenic artery, and occasionally, from a lienal branch In caliber and in length, the artery varies considerably, and in many instances is represented by several branches When typical, it courses along the inferior border of the stomach and anastomoses with the right gastroepiploic artery. *Such visible anastomosis, however, is lacking in 10 per cent of the subjects*, an item of importance in surgical resections of this region Branches of the left gastroepiploic artery include ascending gastric arteries supplying the anterior and posterior surfaces of the stomach and descending epiploic or omental branches, short and long (one of the long ones is the *left epiploic branch* that forms the left limb of the *arc of Barkow* in the posterior layers of the great omentum, the right limb thereof being formed by the *right epiploic artery* from the right gastroepiploic artery); pancreatic rami to the tail of the pancreas, inferior polar arteries to the spleen, which vary in number (1 to 4), length, and size, and often furnish the blood supply to an accessory spleen

SHORT GASTRIC ARTERIES (VASA BREVIA) These vary in number (4 to 10), size, site of origin, and mode of distribution, some of them reaching the esophagus. Collectively, they comprise an upper, middle, and lower group, the latter being the longest The shorter ones arise from the splenic trunk, from the superior splenic terminal artery or its branches, or from a superior splenic polar artery The longer ones arise from the inferior splenic terminal artery and from the left gastroepiploic artery and its branches Through the gastrolienal ligament, the short gastric arteries reach the fundic and cardioesophageal end of the stomach, where they ramify over the anterior and posterior surfaces and anastomose with branches given off by the left gastric, left gastroepiploic, and the recurrent branch of the left inferior phrenic artery after the latter passes under the esophagus in its course to the diaphragm.

SUPERIOR AND INFERIOR SPLENIC TERMINAL ARTERIES They show marked individual variability in regard to their early or late origin from the splenic trunk, their subsequent mode of branching, and the number of penultimate and ultimate lienal branches (7 to 35) arising from them The superior polar artery is a frequent branch (65 per cent) of the splenic trunk or of one of its terminal branches. Arising anywhere from the splenic artery, it varies in length from 2 to 12 cm, in width from 1 to 5 mm, in branches from 2 to 13 It may arise separately from the celiac artery, in which case it constitutes a double splenic artery (a splenica secunda, 2 cases in 300 bodies).

From a terminal divisional point of view, two types of splenic arteries may be distinguished: (1) the *magistral* splenic artery (30 per cent), in which the splenic trunk is long, terminal division occurs near (1 to 2 cm) the hilus, branches are few and large and enter about one-third to one-fourth of the medial surface of the spleen. Superior polar arteries are usually absent, and the left gastroepiploic artery often arises from the inferior terminal artery, (2) the *distributed* splenic artery (70 per cent), in which the splenic trunk is short, lienal branching occurs early, anywhere from the celiac artery to the hilus, and branches are more numerous and smaller in caliber and enter three-fourths of the medial surface of the spleen in different frontal planes Polar arteries are frequent and are distributed to the upper and lower poles, while the left gastroepiploic artery, as a rule, arises from the splenic trunk The magistral splenic artery supplies a compact, usually unnotched spleen The distributed splenic artery is usually associated with a spleen highly notched at its anterior border and having a prominent superior tubercle and a thumb-like inferior lobule Hence, on seeing or feeling the spleen, its type of vascularization can often be predicted or surmised

The Superior Mesenteric Artery. It supplies the third part of the duodenum, a portion of the head, frequently an extensive area of the body of the pancreas, the entire small intestine (jejunum, ileum), and the large intestine up to the left colic flexure It arises from the front of the aorta at an average vertebral level of L1, variations thereof being from the middle

hepatic artery replaced from the left gastric artery; 10 per cent (Fig 1-60B).

3 The left hepatic and middle hepatic arteries—the right hepatic artery replaced from the superior mesenteric artery, 11 per cent (Fig. 1-60C).

4. Only the middle hepatic artery—the right hepatic artery replaced from the superior mesenteric artery, the left hepatic artery replaced from the left gastric artery, 1 per cent.

5 The right, middle, and left hepatic arteries—left hepatic artery small, hence an accessory left hepatic artery from the left gastric artery; 8 per cent (Fig 1-60D).

6 The right, middle, and left hepatic arteries—right hepatic artery small, hence an accessory right hepatic artery from the superior mesenteric artery, etc.; 7 per cent (Fig 1-61A).

7. The right, left, and middle hepatic arteries—small or of usual size. There is an accessory right hepatic artery from the superior mesenteric artery and an accessory left hepatic artery from the left gastric artery, 1 per cent (Fig 1-61B)

8. Combination patterns of a replaced right hepatic artery and an accessory left hepatic artery or, the reverse of this, an accessory right hepatic artery with a replaced left hepatic artery, 2 per cent.

9 Celiac hepatic artery absent—the entire hepatic trunk derived from the superior mesenteric artery, 5 cases (Fig 1-61C)

10 Celiac hepatic artery absent—the entire hepatic trunk derived from the left gastric artery, 1 case (Fig. 1-61D).

The Splenic Artery. The splenic artery (a lienalis) is the largest branch of the celiac artery, arising from the latter, in most instances, just distad to the origin of the left gastric artery In about 25 per cent of subjects, the splenic, hepatic, and left gastric arteries arise from the same point, forming a tripod celiac artery When the dorsal pancreatic, or a middle colic, artery takes origin from the same point, a celiac tetrapod is formed (5 per cent) Aberrantly, the splenic artery may arise only with the hepatic artery, only with the left gastric artery, or with the superior mesenteric artery, thereby constituting different types of celiac axis

More than any other artery, the splenic artery presents individual constitutional variations, especially in regard to number and mode of origin and distribution of its branches, the penultimate and ultimate lienal branches being different in each case. The caliber of the splenic artery varies from 5 to 12 mm, this vessel often being much larger than the hepatic artery. In length, the splenic artery varies from 8 to 38 cm, the average being 13 cm. The instances of extraordinary length are due to the fact that the splenic artery, in adults, is often markedly tortuous (looped, twisted, coiled), a phenomenon noted in old persons by *Leonardo da Vinci*, the causative factor is not yet known. Terminal division of the splenic artery is usually effected in two main branches, the a terminalis superior and the a. terminalis inferior; occasionally an a terminalis media is formed (Fig. 1-59).

The most constant branches of the splenic artery are (1) pancreatic artery, (2) left gastro-epiploic artery, (3) short gastric arteries, (4) superior and inferior terminal arteries and their lienal branches. Inconstant yet frequent branches are the superior and inferior splenic polar arteries, and the accessory left gastric arteries; these are distributed, anteriorly and posteriorly, to the cardioesophageal and fundic regions of the stomach, the posterior often being of large size (Fig. 1-62).

PANCREATIC BRANCHES. They are given off by the splenic artery as it courses along the upper margin of the pancreas. While most of them are small and vary in number, three pancreatic branches are large and have a characteristic distribution, viz., the dorsal pancreatic branch, the a. pancreatica magna, and the a caudae pancreatis (Fig 1-62).

The *dorsal pancreatic branch*, not often mentioned, is a relatively large vessel (1 to 4 mm), distributed to the posterior surface of the pancreas in the neck region, where it can readily be found behind the splenic vein Typically, it gives off two small right branches and one large left branch. Of the right branches, one joins the gastroduodenal artery, the other supplies the uncinate process. Its typical left branch is the transverse pancreatic artery, which courses along the dorsocaudal surface of the pancreas, at the tail end of which it anastomoses with the a pancreatica magna While the dorsal pancreatic branch is predominantly a branch of the first part of the splenic artery (39 per cent), it frequently takes origin from other regional vessels, such as the celiac artery (22 per cent), the superior mesenteric artery (14 per cent), and the common hepatic artery (12 per cent).

The *a pancreatica magna*, the second large pancreatic branch of the splenic artery, arises from the latter at its distal third. After ramify-

ing in the tail of the pancreas, it swerves to the right to anastomose with the transverse pancreatic branch, which it assists in supplying blood to the pancreatic duct.

The *caudal pancreatic artery* is the last large branch of the splenic trunk, although it frequently arises from a terminal branch of the latter or from the left gastroepiploic artery. Entering the tail of the pancreas, it communicates with branches of the a pancreatica magna and the transverse pancreatic artery

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SUPERIOR AND INFERIOR SPLENIC TERMINAL ARTERIES They show marked individual variability in regard to their early or late origin from the splenic trunk, their subsequent mode of branching, and the number of penultimate and ultimate lienal branches (7 to 35) arising from them The superior polar artery is a frequent branch (65 per cent) of the splenic trunk or of one of its terminal branches. Arising anywhere from the splenic artery, it varies in length from 2 to 12 cm, in width from 1 to 5 mm, in branches from 2 to 13 It may arise separately from the celiac artery, in which case it constitutes a double splenic artery (a splenica secunda, 2 cases in 300 bodies).

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The Superior Mesenteric Artery. It supplies the third part of the duodenum, a portion of the head, frequently an extensive area of the body of the pancreas, the entire small intestine (jejunum, ileum), and the large intestine up to the left colic flexure It arises from the front of the aorta at an average vertebral level of L1, variations thereof being from the middle

of L1 to the upper third of L2 in 83 per cent of cases (Anson and McVay). Distance between the origin of the celiac artery and the superior mesenteric artery varies from 1 to 22 mm, being most commonly from 1 to 6 mm (Michels, 1955). Caliber of the superior mesenteric artery varies from 12 to 26 mm, the average being 20 mm (Delmas et al., 1953).

In rare instances, the superior mesenteric artery arises with the celiac artery (in a common celiacomesenteric trunk) or with the splenic artery (lienomesenteric trunk). Commonly, it gives off a replaced or an accessory right hepatic artery (17 per cent); less frequently, the entire hepatic trunk (1.5 per cent, Michels, 4.4 per cent, Daseler et al.), thus forming a hepatomesenteric trunk Very rarely, a hepatic artery along with the splenic artery is given off, forming a hepatolienomesenteric trunk

After its origin from the celiac artery behind the pancreas, the superior mesenteric artery emerges along with the superior mesenteric vein from beneath the pancreas, crosses the uncinate process and the front of the ascending part of the third part of the duodenum to enter the root of the mesentery Here it proceeds downward to the right iliac fossa to within 6 in of the ileocecal junction, where it ends by uniting with the ileal branch of the ileocolic artery.

The constant branches of the superior mesenteric artery are the (1) inferior pancreaticoduodenal, (2) intestinal (12 to 14 in number, jejunal and ileal), (3) middle colic, (4) right colic, (5) ileocolic arteries Inconstant branches frequently met with are the (6) dorsal pancreatic, (7) transverse pancreatic, (8) an accessory or replaced right hepatic (17 per cent) or the entire hepatic, (9) accessory middle colic (10 per cent), (10) the ramus anastomoticus of Bühler, connecting the celiac artery or one of its branches with the superior mesenteric artery or one of its branches. In some instances, the splenic, the gastroduodenal, the superior pancreaticoduodenal, the right gastroepiploic and even the cystic artery may take origin from it.

INFERIOR PANCREATICODUODENAL ARTERY. Predominantly (60 per cent), it arises as a single vessel from the right side of the superior mesenteric artery, less frequently, from the left side of this artery or *from its first or second jejunal branch*. It courses upward behind the head of the pancreas, where it divides into an anterior and posterior branch. The former unites with the superior pancreaticoduodenal artery to form the anterior pancreaticoduodenal arcade, the latter unites with the retroduodenal artery to form the posterior pancreaticoduodenal arcade. Both branches supply rami (three to four) to the third part of the duodenum and pancreas. Surgically, it is important that, in many instances, there are *two* inferior pancreaticoduodenal arteries, the one for the posterior arcade, joining the superior mesenteric artery directly at a much higher level, or uniting with its first or second jejunal branch. In instances, instead of joining the superior mesenteric directly, the inferior pancreaticoduodenal courses upward behind or *through the head of the pancreas* (where it would be vulnerable in resections) to join an aberrant right hepatic from the superior mesenteric artery.

INTESTINAL ARTERIES They comprise two groups, jejunal and ileal. Varying in number from 12 to 14, they arise from the left convex surface of the superior mesenteric artery, the upper ones being larger than the lower. As the intestinal arteries radiate out between the two layers of the mesentery, each artery divides into two branches that communicate with similar branches given off by the branch above and the branch below. In this manner, a series of scalloping primary loops or arcades is formed which, as a whole, runs parallel with the intestine. Through division and union of branches given off by the primary arcades, secondary arcades and, in like manner, tertiary, quaternary, and even a network of quinary loops or arcades, are formed. The most distal, i e , ultimate, arches give off a large number of straight jejunal and ileal branches (*vasa recta*). These do not anastomose but proceed to the gut wall, where each terminal artery divides into an anterior and posterior branch supplying the respective surfaces of the gut, usually in alternate order The vasa recta end as end arteries by forming anastomotic arterial rings In this manner, a continuous vascular network is established through the jejunum and ileum, thereby equalizing the blood supply and allowing for a rapid collateral circulation when, through pressure exerted by peristalsis, any section of the intestine temporarily becomes deprived of its blood supply. Proximally, the vascular network communicates with the inferior pancreaticoduodenal artery, distally, with the terminal

artery, i.e., the last intestinal branch of the superior mesenteric artery.

MIDDLE COLIC ARTERY. It arises from the concave side of the *superior* mesenteric artery at the lower border of the pancreas, a bit below the origin of the inferior pancreaticoduodenal artery. Entering the right half of the transverse mesocolon, it divides, at a variable distance from the gut wall (5 to 7 cm), into two branches, one of which courses to the right to anastomose with the ascending branch of the right colic artery while the other passes to the left to anastomose with the ascending branch of the left colic artery from the inferior mesenteric artery. Through subsequent branching, the primary and secondary arches are formed, from which terminal straight branches (vasa recta) are given off to the entire transverse colon, except its distal left end (the splenic flexure).

The typical pattern of the middle colic artery has many important variants, among these being (1) its occasional origin from the celiac artery, or its absence, in which case it is replaced by a branch of the left colic artery, (2) the presence of an accessory middle colic artery (10 per cent) (this artery, derived from the superior mesenteric artery a bit above the normal vessel or from the celiac artery via the dorsal pancreatic artery, courses through the transverse mesocolon in the avascular area of Riolan to become distributed to the distal third of the transverse colon), (3) origin from the middle colic artery of the dorsal pancreatic or transverse pancreatic artery, a frequent pattern (14 per cent); (4) instead of bifurcation, division into three, four, or more branches, the proximal part of the transverse colon being supplied by one of the right branches, when the right colic artery is absent.

RIGHT COLIC ARTERY. This artery is markedly varied in its origin and distribution and is frequently (18 per cent) absent, or not identifiable as a separate vessel, being replaced by a branch of the middle colic or ileocolic artery. Typically, it arises from the concave side of the superior mesenteric artery, either as a separate vessel, or via a common trunk of variable length that divides into the right colic and ileocolic arteries (33 per cent). Nearing the ascending colon, the right colic artery divides into two main branches, an ascending one that anastomoses (frequently, very meagerly) with a descending branch of the middle colic artery, and a descending one that anastomoses with the ascending or colic branch of the ileocolic artery.

Aberrancies of the right colic artery, as observed by Steward and Rankin, comprise (1) its absence in 18 per cent of cases; (2) origin from *superior mesenteric artery* (40 per cent), middle colic artery (30 per cent), or ileocolic artery (12 per cent). Variants thereof are illustrated in Anson's *Atlas of Human Anatomy*.

ILEOCOLIC ARTERY. Typically, it arises from the superior mesenteric artery, either separately or via a common trunk with the right colic artery. At a variable distance from the colon, it divides into two branches, an ascending branch that anastomoses with a descending

posterior cecal, (4) ileal, (5) appendicular. The colic branch ascends and marks the beginning of the *marginal artery of Drummond.* The anterior cecal branch courses through the superior cecal fold. The posterior cecal branch passes behind the ileum. The ileal branch courses in the mesentery, where it unites with the end, i.e., last, intestinal branch of the superior mesenteric artery, forming a single or double arc, from which several terminal branches (vasa recta) are given off to the last 6 in. of the ileum. The appendicular artery usually arises from the ileal branch of the ileocolic or end-branching point of this vessel and, after passing behind the ileum, courses in the free edge of the mesoappendix, an anastomosis of the artery with regional blood vessels being sparse. For variants of origin of the appendicular artery, see Anson's *Atlas of Human Anatomy.*

Routes of Collateral Circulation in the Upper Abdominal Organs. No region in the body presents more diversified routes of blood supply to a specific organ than the organs lying above the transverse colon. The pancreas lies in three interlocking arterial circles formed by the hepatic, splenic, and superior mesenteric arteries, none of which is the sole blood supply to the organ. The liver may have three separate sources of blood supply: from the celiac hepatic artery, the superior mesenteric artery (via a replaced or accessory right hepatic artery), and the left gastric artery (via a replaced or accessory left hepatic artery). The stomach receives its main blood supply from six different

sources, viz., right and left gastric arteries, right and left gastroepiploic arteries, short gastric arteries from the splenic, esophageal, and fundic branches from the recurrent branch of the left inferior phrenic artery. Predominantly, however, six other arteries are involved in its blood supply, viz., the gastroduodenal, superior pancreaticoduodenal, supraduodenal, retroduodenal, transverse pancreatic, and dorsal pancreatic arteries. The great omentum, appended to the stomach and to the pancreas, has a rich vascular supply and, through the arc of Barkow in its posterior layer, is well adapted to function as a seat of compensatory circulation for both the liver and spleen, when either the hepatic or the splenic artery is occluded. Because of the relational anatomy, it is quite obvious that the collateral pathways for the upper abdominal organs are effected mainly by the splenic artery. Splenic collateral pathways comprise 3 routes inside the system of the splenic artery, and 12 outside it. These, like those for the liver, were described for the first time in Michels' *Blood Supply and Anatomy of the Upper Abdominal Organs: With a Descriptive Atlas*.

Arterial Collateral Pathways to the Liver. While textbooks of anatomy describe the collateral routes of return of the portal blood to the heart when the portal vein or the hepatic capillaries (sinusoids) become occluded in diseases of the liver, no mention is made of the collateral routes by which arterial blood may reach the liver when the hepatic artery is ligated or becomes obstructed. That some kind of compensatory circulation to the liver can be established is obvious from the many cases of survival of patients with portal cirrhosis in whom the hepatic artery was ligated with beneficial results (Rienhoff, 1951), and of patients with gastric carcinoma in whom the entire celiac axis was removed along with the stomach, spleen, and the greater part of the pancreas (Appleby, 1953). While the anatomic rationale for the survival of these patients is, as yet, not clear, there are, *de facto*, 26 possible collateral routes by which arterial blood may reach the liver when the celiac common hepatic artery is ligated (Fig. 1-62).

The Inferior Mesenteric Artery. Considerably smaller than the superior mesenteric artery (7 to 15 mm, average 10 mm, Delmas et al., 1953), it arises from the front of the aorta 5 to 6 cm before the bifurcation of the latter. The vertebral level of its origin varies from the middle of L2 to the disk between L3 and L4, most frequently being at the middle of L3 (Taniguchi, 1931). Descending obliquely to the left iliac fossa, it divides into an ascending and descending branch at a variable distance from the gut wall of 3 to 10 cm. The former unites with the left descending branch of the middle colic artery; the latter, after giving off two to four sigmoid arteries and a fairly constant rectosigmoid artery, becomes, beyond the iliac vessels, the superior rectal artery (hemorrhoidal, caliber 7.5 mm, Delmas); this, at the upper border of the rectum, divides into right and left branches which anastomose with the middle rectal artery (hemorrhoidal) from the hypogastric artery. In about two-thirds of subjects, the ascending branch of the left colic artery supplies the distal third of the transverse colon (splenic flexure). It may be represented by two vessels; the one coursing parallel with the colon constitutes the marginal artery. In many instances, an additive branch given off by the first part of the inferior mesenteric artery, ascends to the left colic flexure, effecting an anastomosis with the middle colic artery in its course (*arc of Riolan*).

SUDECK'S CRITICAL POINT. Many conflicting reports have been made regarding the mode of vascularization of the lower part of the sigmoid colon and the upper fifth of the rectum, in particular regarding the existence and adequacy of an anastomosis between the lowest branch to the sigmoid colon and the superior rectal artery. At present, it is generally agreed that transillumination of the mesentery at operation is the best method of ascertaining the actual vascular pattern of the blood supply between the rectosigmoid artery and the rectum (Bacon and Smith, 1948).

MARGINAL ARTERY OF DRUMMOND. Since radical surgical procedures on the colon are always fraught with the danger of sepsis, abdominal peritonitis, and gangrene in the wall of the bowel from ischemia, knowledge of the marginal artery and its variability is of great importance to the surgeon. As usually interpreted, the *marginal artery of Drummond* (1914) is made up by the end of the superior mesenteric artery and the anastomotic adjacent branches of the ileocolic, right colic, middle colic, upper left colic, and lower left colic (sigmoid) arteries. The arrangement of the blood vessels to the colon is comparable with that of a rubber-tired wheel having few irregularly spaced spokes, the spokes represent the main colic arteries while the rubber tire represents the con-

tinuous uninterrupted marginal artery. It is generally assumed that if the marginal artery is left intact while tying off an individual colic artery, viability of the colon is not endangered. Gangrene after operation will not eventuate, for the marginal artery (through its anastomotic primary and secondary loops or arcades) can be relied upon to furnish the necessary blood supply. In about 5 per cent of subjects, however (Steward and Rankin), the marginal artery is discontinuous, thus endangers the collateral circulation, which is between (1) the ileocolic and right colic arteries, (2) middle colic and superior left colic arteries, and (3) inferior left colic and superior hemorrhoidal arteries (10 per cent, Drummond).

Blood Supply of the Kidneys and Suprarenal Glands. A point rarely stressed is the intimate relation of the renal arteries to the suprarenal glands and of the suprarenal arteries to the kidneys, actually, the vascular supply of the two organs is, in most instances, intimately intertwined. Frequently, the renal artery gives off from two to five twigs to the suprarenal gland, while inferior suprarenal arteries stemming from the aorta or renal often supply from one to four twigs to the superior pole of the kidney and its fat body (capsular branches) (Figs 1-63, 1-64).

More than for any other organ in the body, the vascularization of the kidney has been the topic of repeated anatomic investigation, statistical analysis, and description For pioneer discoveries of the structure of the kidney and its intraorganic vascular arrangement, the reader is referred to a classical monograph of Hou-Jensen (1930). The most extensive and complete assembly of the world's literature on the renal and suprarenal blood supply, with a critical review thereof, is that published by Merklin and Michels (1958). The article contains a tabulated statistical analysis of renal arterial variations as observed by 45 investigators on a total of 10,967 kidneys along with observations of their own on 185 kidney dissections

Knowledge of the renal and suprarenal arteries is essential to the surgeon, not only in nephrectomy, but also in the diverse modern operative procedures on the kidney, viz., nephrotomy, heminephrectomy, nephrostomy pyelotomy [illegible] to speak [illegible] performe [illegible] more, ad [illegible] knowledge of the varied patterns of the renal blood supply is needed for competency in diagnostic radiology, i.e., in reading and correctly interpreting roentgenographic records of a distorted pelvis and complex hilar arterial and venous patterns made by excretion urography (pyelograms) and renal arteriography (renal angiograms). The striking usefulness of the latter in preoperative diagnosis of hydronephrosis has been demonstrated by Edsman (1954). Knowledge of varied possible arterial renal patterns is helpful to those working with retroperitoneal pneumography, i.e., use of air or oxygen for visualization of the renal complex, especially for the detection of a horseshoe kidney (Fetter, Varano, and Ayres, 1956).

Suprarenal Arteries. Contrary to the usual description, the suprarenal *arteries are not* represented by three stem arteries derived *singly from the inferior* phrenic artery, aorta, and renal artery, but comprise for each gland, in every body, a variable number of arteries (*10 to 60*) that encompasses the suprarenal gland *in an arterial circle.* The latter is well anastomosed in the fetus and in young individuals (*Gérard*) but in the adult is reduced to slender anterior and posterior marginal branches that are in relation with rami derived from the regional arteries supplying the gland.

On the basis of their origin and distribution, the suprarenal arteries may be classified into three groups, viz., the superior, middle, and inferior The *superior suprarenal arteries* comprise from 3 to 30 twiglike branches derived from the inferior phrenic artery. From 3 to 5 of these stem from its proximal portion that courses medial to the gland, the remaining stem from its posterior division (after bifurcation), which courses in concave fashion above the gland. As slender rami, arranged in seriation like the teeth of a comb, the suprarenal arteries reach the medial and superior border of the gland to become distributed to its anterior and posterior surfaces. Many of the arteries ramify superficially or bifurcate before entering the parenchyme, others anastomose with marginal branches In some instances, some of the superior suprarenal arteries arise directly from the aorta or celiac artery, or from a second inferior phrenic artery (Fig 1-63)

The middle suprarenal artery may be regarded as the hilar artery It is usually (85 per cent, Gérard) a single vessel and, pre-

sources, viz., right and left gastric arteries, right and left gastroepiploic arteries, short gastric arteries from the splenic, esophageal, and fundic branches from the recurrent branch of the left inferior phrenic artery. Predominantly, however, six other arteries are involved in its blood supply, viz., the gastroduodenal, superior pancreaticoduodenal, supraduodenal, retroduodenal, transverse pancreatic, and dorsal pancreatic arteries. The great omentum, appended to the stomach and to the pancreas, has a rich vascular supply and, through the arc of Barkow in its posterior layer, is well adapted to function as a seat of compensatory circulation for both the liver and spleen, when either the hepatic or the splenic artery is occluded Because of the relational anatomy, it is quite obvious that the collateral pathways for the upper abdominal organs are effected mainly by the splenic artery. Splenic collateral pathways comprise 3 routes inside the system of the splenic artery, and 12 outside it These, like those for the liver, were described for the first time in Michels' *Blood Supply and Anatomy of the Upper Abdominal Organs· With a Descriptive Atlas*

Arterial Collateral Pathways to the Liver. While textbooks of anatomy describe the collateral routes of return of the portal blood to the heart when the portal vein or the hepatic capillaries (sinusoids) become occluded in diseases of the liver, no mention is made of the collateral routes by which arterial blood may reach the liver when the hepatic artery is ligated or becomes obstructed That some kind of compensatory circulation to the liver can be established is obvious from the many cases of survival of patients with portal cirrhosis in whom the hepatic artery was ligated with beneficial results (Rienhoff, 1951), and of patients with gastric carcinoma in whom the entire celiac axis was removed along with the stomach, spleen, and the greater part of the pancreas (Appleby, 1953) While the anatomic rationale for the survival of these patients is, as yet, not clear, there are, *de facto*, 26 possible collateral routes by which arterial blood may reach the liver when the celiac common hepatic artery is ligated (Fig. 1-62).

The Inferior Mesenteric Artery. Considerably smaller than the superior mesenteric artery (7 to 15 mm, average 10 mm, Delmas et al., 1953), it arises from the front of the aorta 5 to 6 cm before the bifurcation of the latter. The vertebral level of its origin varies from the middle of L2 to the disk between L3 and L4, most frequently being at the middle of L3 (Taniguchi, 1931). Descending obliquely to the left iliac fossa, it divides into an ascending and descending branch at a variable distance from the gut wall of 3 to 10 cm The former unites with the left descending branch of the middle colic artery; the latter, after giving off two to four *sigmoid arteries* and a fairly constant *rectosigmoid artery*, becomes, beyond the iliac vessels, the *superior rectal artery* (hemorrhoidal, caliber 7.5 mm, Delmas); thus, at the upper border of the rectum, divides into right and left branches which anastomose with the middle rectal artery (hemorrhoidal) from the hypogastric artery. In about two-thirds of subjects, the ascending branch of the left colic artery supplies the distal third of the transverse colon (splenic flexure) It may be represented by two vessels, the one coursing parallel with the colon constitutes the marginal artery. In many instances, an additive branch given off by the first part of the inferior mesenteric artery, ascends to the left colic flexure, effecting an anastomosis with the middle colic artery in its course (*arc of Riolan*).

SUDECK'S CRITICAL POINT Many conflicting reports have been made regarding the mode of vascularization of the lower part of the sigmoid colon and the upper fifth of the rectum, in particular regarding the existence and adequacy of an anastomosis between the lowest branch to the sigmoid colon and the superior rectal artery At present, it is generally agreed that transillumination of the mesentery at operation is the best method of ascertaining the actual vascular pattern of the blood supply between the rectosigmoid artery and the rectum (Bacon and Smith, 1948)

MARGINAL ARTERY OF DRUMMOND Since radical surgical procedures on the colon are always fraught with the danger of sepsis, abdominal peritonitis, and gangrene in the wall of the bowel from ischemia, knowledge of the marginal artery and its variability is of great importance to the surgeon As usually interpreted, the *marginal artery of Drummond* (1914) is made up by the end of the superior mesenteric artery and the anastomotic adjacent branches of the ileocolic, right colic, middle colic, upper left colic, and lower left colic (sigmoid) arteries The arrangement of the blood vessels to the colon is comparable with that of a rubber-tired wheel having few irregularly spaced spokes, the spokes represent the main colic arteries while the rubber tire represents the con-

variably, it is distributed to the anteromedial surface of the gland, which it reaches by passing through or behind the celiac ganglion. On the right side, it invariably passes behind the inferior vena cava. Its terminal branches comprise an ascending and a descending medial marginal branch, a hilar branch, several posterior branches, and, in many instances, an anterior superior adipose capsular branch to the kidney. Most frequently, the middle suprarenal artery arises from the aorta, but in many cases, it takes origin from the proximal part of the inferior phrenic artery, from the first part of the renal artery, or from an accessory *upper renal* (superior polar) artery or from the *celiac* trunk. The artery is often double, in *which* case the accessory one may have any of the varied sites of origin previously listed. At times, it is lacking, being replaced by a superior or inferior *suprarenal artery*.

The *inferior suprarenal arteries* are the *most* important, since they supply the thickest and largest part of the gland, entering the latter on its posterior and inferolateral *surfaces*. In about 66 per cent of subjects, the inferior suprarenal artery is single (Gérard) and, predominantly, arises from the proximal part of the renal artery, or from an accessory upper renal artery, or one of its extrahilar branches. Its *terminal* branches comprise anterior and posterior marginal branches, and a basal *fat branch* distributed to the fat interposed between the kidney and the suprarenal gland, which in the adult varies from 0.5 to 1 cm in thickness (Iwanow, 1927) but is lacking in the newborn, as ascertained by the author in many dissections.

Aberrantly, the inferior suprarenal artery may arise from the aorta, just above or below the origin of the renal artery, from the middle or distal part of the renal artery, from the lower of dual renal arteries, from an accessory *or superior* polar renal artery, from a trunk division of the renal artery, from the testicular or the ovarian artery, from the inferior phrenic artery itself, or in a common trunk with *the middle* suprarenal artery from the aorta or renal artery. Frequently (23 *per cent*, Gérard), the inferior suprarenal artery is double, one arising from the aorta, the other from the renal artery near the hilus of the kidney or from an accessory renal artery or *one* of its branches. In many cases, multiple inferior suprarenal arteries are present. These may spring from the varied sites of origin listed for the single type and, usually, branch before entering the gland. Commonly, the anterior superior capsular adipose branch to the kidney (a collateral of the renal artery in most instances) gives off from 3 to 10 twigs to the inferior and lateral surface of the gland. This branch may arise separately from the aorta, uppermost of dual renal arteries, inferior phrenic artery, or in a common trunk with the testicular *or the ovarian* artery. Unusual patterns are cases in which an inferior phrenic artery stemming from the aorta supplies all the *superior, middle, and inferior* suprarenal arteries and, in addition, a renal polar artery, a capsular branch to the kidney, and the testicular or ovarian artery (pattern nearly thus in Fig. 1-64B).

Renal Arteries. In most instances the kidney is supplied by one renal artery *(72 per cent of* 11,000 kidneys reported in the literature, Merklin and Michels). *It arises* from the lateral side of the aorta and gives off no other branches than those entering the hilus or its borders. Atypically, *parenchymatous* branches may arise from *the single renal trunk*, from its anterior or posterior division, or from one of its terminal rami. *Leaving* the renal artery, these branches become *distributed* variously to the upper or lower pole of the kidney (renal polar branches), *to the* anterior or posterior lip of the hilus, or *to any external (extrahilar)* surface of the kidney or to its fatty capsule. Constant branches of the single renal artery are the inferior suprarenal arteries (one to three). An inconstant, yet frequent, branch is the testicular artery *or ovarian* artery, *being the component of the renal pedicle in 16 per cent of cases* on the *right side* and 34 per cent on the left (Notkovich, *183 cases, 1956*). Another inconstant *branch is the* inferior phrenic artery, especially from the right renal *artery*.

Most commonly, *the* vertebral level of origin of the renal *arteries is at the* lower third of L1, at the disk between L1 *and L2*, and at the cranial third of L2 (Heidsieck). The right and left renal arteries may have the same *height* level (32 per cent of cases), *but that of the* right is commonly higher (47 *per cent*), while that of the left *is* less commonly so (21 per cent, Taniguchi). A *single* renal artery may be present on the *right*, with multiple renal arteries (two, three, *four*) on the left, and vice versa; there is no sex or racial difference in this respect (Fig. 1-64).

The right renal artery is longer than the left and, nearly invariably, courses behind the in-

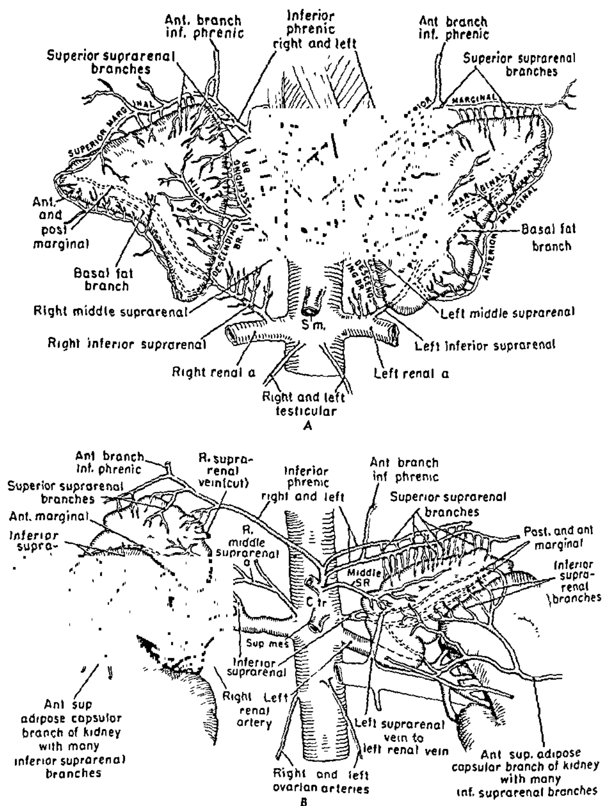


Fig. 1-63. A. Composite drawing of the blood supply to the suprarenal gland. General scheme of suprarenal arteries comprises (1) inferior suprarenal arteries which have (a) slender collaterals and (b) terminals composed of marginals (anterior and posterior) and a basal fat branch. (2) middle suprarenal artery which has (a) slender collaterals and (b) terminals (ascending, descending, hilar, posterior); (3) superior suprarenal arteries derived from the phrenic trunk and its posterior division. B Anterior superior adipose capsular branch of kidney, female, 52 years old. Note intimate relation of the blood supply of the suprarenal gland with that of the kidney. Superior suprarenal arteries comprise a variable number of twiglike branches derived from the single right and double left inferior phrenic artery. Right middle suprarenal artery stems from the aorta, left from the celiac artery. Right inferior suprarenal artery arises from a superior renal polar artery, the left from the aorta. On both sides the anterior superior adipose capsular branch gives off numerous inferior suprarenal branches. *(Modified from Gérard, 1913.)*

ferior vena cava When multiple renal arteries are present, the caudal ones often take a precaval course The length of the right renal artery, from its aortic origin to its division point, varies from 0 5 to 8 cm, that of the left, varies from 0.5 to 6 cm (Levi). The caliber of the right and left renal arteries is usually the same, the average diameter being 5 5 mm, with variations from 4 to 7 mm (Hou-Jensen). The diameter of an accessory, i e, supernumerary renal, artery varies from 1 to 6 mm and depends on the extent of the kidney area supplied, the superior and inferior renal polar arteries often being one-half the size of the main renal artery.

As with the splenic artery, the renal artery may break up into its terminal branches early, i e, shortly after its origin from the aorta, or late, i e, near and in the hilus of the kidney, thus allowing a classification of renal arteries into two main types, viz, the *distributed* (with a short stem) and the *magistral* (with a long stem), these varieties being comparable to similar divisions of the splenic artery Division of the right and left renal arteries need not be symmetric, for frequently the pattern is of the distributed type on the right side, and the magistral on the left, or vice versa.

In most instances, division of the renal artery into a ventral and dorsal trunk occurs late, i e, at an equal distance between the aorta and hilus or in the neighborhood of the hilus Division of the renal artery may be precocious occurring immediately after its origin from the aorta, thereby giving the impression of the presence of dual renal arteries The number of subsidiary or principal branches of the renal trunk varies from two to five. Most commonly, four principal branches enter the parenchyma. Three of these derive from the ventral trunk, course ventral to the pelvis, and were termed by Levi the *anterior superior, anterior medial, and anterior inferior rami.* The fourth main trunk, a continuation of the posterior trunk, courses posterior to the pelvis and was accordingly termed the *retropyelic ramus.* As a sequence to the discovery of Graves (1954), by means of plastic casts, that the kidney is a segmental organ composed of five segments (apical, upper, middle, lower, posterior), the three terminal branches of the anterior division of the renal artery are now known as the *upper, middle, and lower segmental branches,* since they supply these respective segments. The posterior division, a continuation of the renal artery, supplies the posterior segment. The artery to the apical segment has a varied origin, most commonly being derived from the anterior division of the renal artery. A fuller discussion of the correlation between the five renal segments and the specific arteries supplying them will be given later

Right renal artery, after giving off the posterior segmental branch, supplies the apical, upper, middle, and lower segmental branches *Superior suprarenal* arteries, SSR, from phrenic arteries, *RIP, LIP,* are distributed to medial and superior surfaces of the suprarenal gland. Middle suprarenal artery, MSR, on right, from renal, on left, from phrenic. Inferior suprarenal arteries, ISR, arise by two stem arteries from renal artery on right, and by four stem arteries, on the left, these being one from celiac artery, CTr, two from renal artery, and one from testicular artery, TA On both sides, they give rise to adipose capsular branches, CAPA, that are accompanied by capsular veins *An inferior* suprarenal artery may cross in front of the left renal vein, as is often the case with the left gonadal artery. B Sixty-year-old man *Strikingly aberrant* origin of the blood supply to right side of diaphragm, most of right suprarenal gland, and to upper pole of kidney from an inferior phrenic artery, RIP, derived from aorta, at a renal level. In instances, this kind of an inferior phrenic artery arises from the renal trunk itself, and severance thereof, in nephrectomy, would result in complete necrosis of the suprarenal gland. Following Graves's terminology, the right renal artery, after giving off the posterior segmental branch, purportedly, gives rise to the upper, middle, and lower segmental branches, the latter subdividing into three rami Left renal artery, after giving off the posterior segmental branch (with [illegible] rise to the apical, upper [illegible] separate phrenic ar [illegible] gives MSR, stems from ce [illegible] from celiac ganglion wh [illegible] they supply inferior [illegible] artery, [illegible] the arteries passing through the (superior polar, phrenic, and an aortic capsular branch), on left, they arise from renal artery and inferior suprarenals, ISR, on right stem from three sources its branches (After Merklin and Michels)

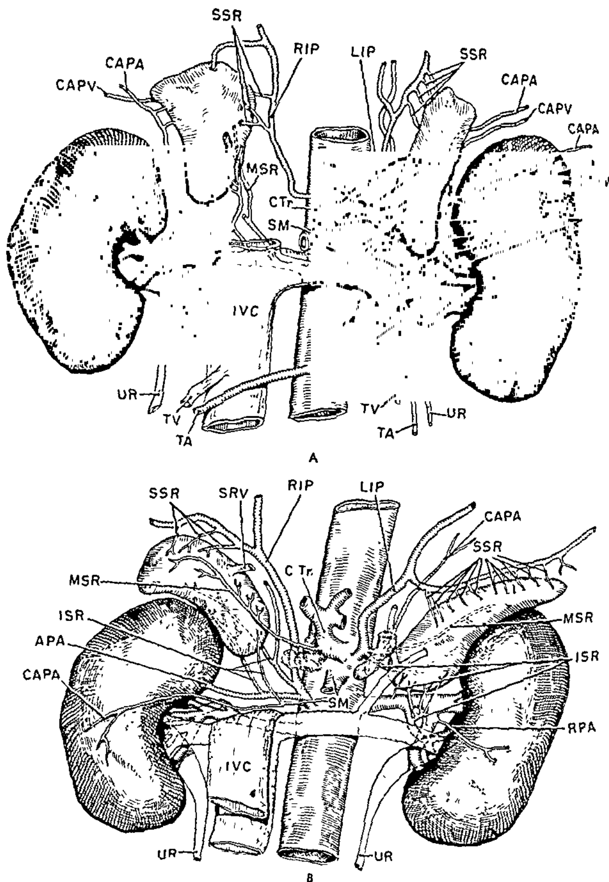


Fig 1-64. A Sixty-four-year-old man. Single right and double left renal arteries, the latter crossing each other. Upper left renal artery enters caudal end of hilus and, in accord with the terms of Graves, purportedly supplies the lower segmental branch Lower renal artery enters the cranial end of hilus and supplies the apical, upper, middle, and posterior segmental branches.

Supernumerary Renal Arteries. Diverse and confusing terms have been employed in the literature to designate the supernumerary renal arteries, with the result that statistical estimates of their percentage occurrence varies from 15 to 60 per cent (Poynter). The confusion is worsened by the fact that some percentages are based on the number of kidneys studied, others on the number of bodies investigated, and still others on the number of body sides examined In the following account, a supernumerary renal artery comprises the following branches. (1) an additional separate aortic renal, (2) an aortic superior polar, (3) an aortic inferior polar, (4) a renal superior polar, (5) a renal inferior polar, or (6) a renal derived from other sources, such as the inferior suprarenal artery, inferior phrenic artery, testicular (ovarian) artery, inferior mesenteric artery, bifurcation point of the

shoe kidney.

Supernumerary renal arteries occur in about 30 per cent of kidneys, this being the average inci-

ally Only a few cases with five or six renal arteries

in this respect. Variants in the renal arteries of both kidneys in the same body occur in about 16 per cent of subjects (Kolster, Hellstrom). *In sides* examined, supernumerary renal arteries occur in 32 per cent, while supernumerary veins are found *in only* 14 per cent (Anson et al).

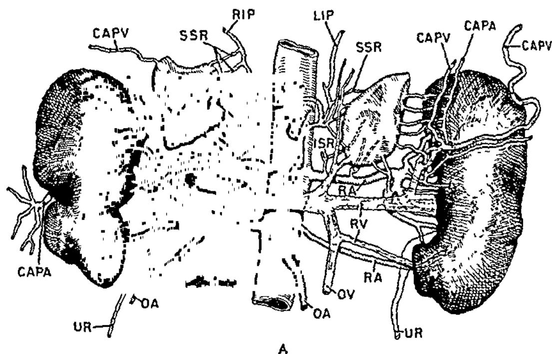
The shortest and most readily understood concept of *multiple* renal arteries may be expressed by saying that two, three, or four right renal arteries may be associated with two, three or four left renal arteries, and *vice versa* When dual or when segmentally arranged (right and left), they tend to have the same caliber. When dispersed to the upper or lower extremity of the kidney, they predominantly have a smaller caliber than the aortic hilar renal arteries Multiple renal arteries may be given off by the aorta from the level of the superior mesenteric artery to that of the inferior mesenteric artery or as high as the aortic diaphragm and as far inferior as the hypogastric artery. The distance between the aortic origin of the supernumerary renal arteries varies considerably, the shortest being 0.7 cm, the longest 8 9 cm, the average 2.79 cm (Anson et al.).

As a guide to translumbar arteriography and *to assure a complete filling of all renal arteries with a contrast medium*, it is important to know that the vertebral level of origin of supernumerary renal arteries may vary from T11 to L4. When triple or quadruple, they may be segmentally arranged along L2, L3, and L4. In their course to the kidney, the upper supernumerary renal arteries may be retrocaval, the lower ones precaval. Usually, as they course transversly, they are parallel and enter the hilus and kidney in the sequence of their origin, but, in instances, the upper aortic accessory renal artery crosses the lower ones to reach the hilus.

Dual renal arteries (Fig. 1-63) from the aorta to the hilus occur rather frequently (10 per cent of 11,000 kidneys reported in the literature). They may arise contiguously, side by side, one in front of the other, or they may be spaced far apart, in the latter instance, they enter the extreme ends of the hilus Dual renal arteries are frequently represented by a pattern, in which, in addition to the main aortic hilar renal artery, there is a superior or inferior aortic or renal polar artery. Very rarely, the lower of dual renal arteries arises from the bifurcation point of the aorta or from the common iliac artery. In dual renal arteries, both may pass in front of the pelvis, or the upper one may pass behind, the lower one in front of, the pelvis, or partly in front of it and partly behind it. The upper renal artery may cross the lower one, then cross the ureteropelvic junction to reach the inferior pole of the kidney (Fig. 1-64)

Triple hilar renal arteries derived from the aorta are, relatively considered, infrequent (1 to 2 per cent of cases). The pattern of triple renal arteries, in which two are hilar and of aortic origin, and the third is either a superior or lower polar artery,

each segment having its own artery with no collaterals Dissection sketches. 1, Typical pattern showing four segmental branches; the fifth (apical) arises inside kidney, most likely from upper segment 2, Four segmental branches arising from same point, apical artery again being intrarenal in origin 3, Four segmental branches from main renal artery, apical artery, and a branch of upper segmental artery, as most commonly the case (Graves). Second hilar branch from aorta becomes lower segmental artery, as is usual with double hilar arteries 4, Late origin of posterior segmental branch and a separate origin from aorta of the apical branch. (*After Merklin and Michels.*)



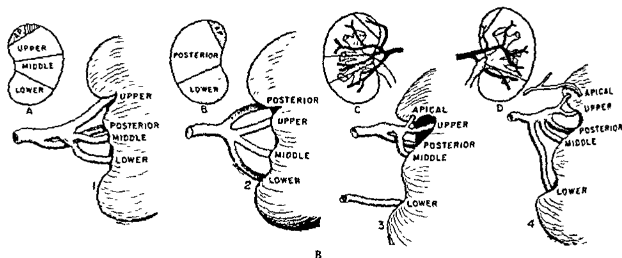


Fig. 1-65. A *Seventy-nine-year-old patient Bilateral dual renal arteries segmentally arranged and hilar in entry Lower left renal artery could be mistaken for an inferior polar artery. Purportedly, it is the lower segmental branch of Graves. The upper left renal artery is of the distributed type and, following Graves' terminology, supplies, in sequence, the apical, upper, posterior, and middle segmental branches Upper right renal artery, after giving off the posterior segmental branch, supplies the upper and middle segmental branches, and, via a superior suprarenal artery, gives off a slender polar (apical) branch Lower right renal artery supplies the lower segmental branch, which, here, divides into its anterior and posterior branches outside the kidney, such division, usually, being intrarenal (Graves). Superior suprarenal arteries, SSR, s'em from the phrenic arteries RIP, LIP, which arise from left side of aorta, via a common trunk. Inferior suprarenal arteries, ISR, arise variously from upper renal arteries, there being three main stems on the left, and one on the right Note copious blood supply to lateral surface of left suprarenal gland, furnished by rami from capsular adipose branches, CAPA, one of them passing through a hiatus in a tributary from capsule to renal vein. Note also emergence of capsular veins from right kidney and origin of right ovarian artery from renal artery, left from aorta. B. Correlation of terminal renal branches with the five segments of the kidney. Sketches A, B, C, and D are modified after Graves (1954, 1956). 1, 2, 3, and 4 are dissection sketches. A. Anterior view of left kidney; B, posterior view. Kidney segments comprise apical, upper, middle, lower, and posterior, only the apical and lower being represented on both anterior and posterior planes. C and D. Anterior and posterior views of kidney showing intrarenal segmental distribution of renal branches.*

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Supernumerary renal arteries occur in about 30 per cent of kidneys, this being the average incidence in 11,000 kidneys recorded in the literature (Merklin and Michels, 1958). They may be double, triple, or quadruple, either unilaterally or bilaterally. Only a few cases with five or six renal arteries have been reported Supernumerary renal arteries occur with equal frequency on the right or left side, and there is no significant sex or racial difference in this respect. Variants in the renal arteries of both kidneys in the same body occur in about 16 per cent of subjects (Kolster, Hellstrom). In sides examined, supernumerary renal arteries occur in 32 per cent, while supernumerary veins are found in only 14 per cent (Anson et al)

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occurs rather frequently. The superior or intermediate of the triple renal arteries may supply a superior polar or a suprarenal branch, the inferior may give off the testicular or ovarian artery, or an inferior polar branch. *Quadruple hilar aortic renal arteries* do occur, but reports of them have been few. In the usual quadruple pattern, the four renal arteries arise from the aorta in segmental sequence, their point of origin being from that of the superior mesenteric artery to that of the inferior mesenteric artery (Anson) The upper two renal arteries may have a postcaval course; the lower two, a precaval one The upper two may pass in front of the pelvis, the lower two behind it. Four renal arteries to the kidney can be effected by a variety of combinations, such as two hilar and two polar, three hilar and one polar, three polar and one hilar. The four renal arteries, occasionally, have the same caliber, but more frequently only one of them is large, the others are smaller and are distributed to the upper or lower extremity of the kidney.

SUPERIOR POLAR ARTERIES. They are usually single and arise separately from the aorta (7 per cent of 11,000 kidneys) or as a branch from the proximal, middle, or distal portion of the renal artery (12 per cent) They may be double or triple, unilaterally or bilaterally, with a varied aortic or renal source of origin for each. Often they arise from an inferior suprarenal artery or from its adipose capsular branch to the kidney. In some instances, they arise from the inferior phrenic artery or from the superior mesenteric artery. Frequently, they give off several branches to the suprarenal gland, a fact to be remembered in removal of the latter (Fig. 1-63).

Surgically, superior polar arteries present many hazards They are often high and cryptically concealed and, accordingly, may be mistaken for strands of connective tissue of an ordinary renal pedicle When inadvertently torn, they produce massive hemorrhage, at times immediately fatal (Eisendrath) When they are ligated, anemic infarcts are produced in the devascularized area with resultant necrosis, for renal arteries are, like the hepatic and splenic ones, *end arteries* in the strictest sense.

INFERIOR POLAR ARTERIES They are prevailingly single and are derived either from the aorta (5.5 per cent) or as a branch of the renal artery (1.4 per cent of 11,000 kidneys) Occasionally, they take origin from the suprarenal, common iliac, and superior mesenteric arteries They may have a high origin from the aorta, even from its posterior hidden surface, then cross lower renal arteries to reach the inferior extremity of the kidney. They may be double, one arising from the aorta, the other from the renal artery, or the two may arise from either source. They may or may not be accompanied by a vein; usually they are not.

Clinically and surgically, the inferior polar arteries are extremely important, being a fundamental anatomic factor in the etiology of *hydronephrosis*. An anomalous blood vessel, such as the inferior polar artery, may cause renopelvic distention by constricting the upper ureter or ureteropelvic junction with intermittent abdominal pain, as a sequence to retained urine. This clinical entity has been verified anatomically and corrected surgically by severance of the obstructing vessel in thousands of cases.

HORSESHOE KIDNEY. This type of kidney was first described by Bérenger de Carpi (1522) as the *ren unguliformis*. Data on its incidence vary considerably

Lipshutz and Hoffman (1918), in an analysis of 70,502 cases of fused kidneys reported in the literature, noted that 105 were horseshoe kidneys. Fetter et al (1956), in an analysis of 4,093 autopsies, found 12 cases (1:345), with a sex incidence of 84 per cent for males and 17 per cent for females In urographic examinations of 13,080 subjects, Lowsley (1952) found 46 cases in pyelograms (1 284), while Dees (1941) found 4 cases in pyelograms in 1,410 patients (1:352).

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Both types of fused kidneys have strikingly aberrant renal arteries, the number of which varies from two to six They may be derived variously from the aorta, common iliac artery, middle sacral artery, external and internal iliac artery, superior and inferior mesenteric arteries, and the bifurcation point of the aorta, the isthmus, in many instances, having a separate blood supply Fetter et al demonstrated the various methods now employed to detect them by x-ray diagnosis scout film, intravenous urography, retrograde pyelography, retroperitoneal pneumography and pyelography, and the pyelographic angle of Gutierrez For illustrations of

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Correlation of the Renal Arteries to the Segmental Division of the Kidney. In an investigation of 70 plastic corrosion casts made of autopsy kidneys and on the basis of 60 renal arteriograms made on them, Graves (1954, 1956), for the first time, gave evidence that the kidney, like the lung and liver, is a segmental organ The parenchyma of every kidney is divisible into five segments. the apical, upper, middle, lower, and posterior The apical segment occupies the medial side of the upper pole, mainly on its anterior surface, a bit of it being in the posterior plane The upper and middle segments lie in the anterior plane The lower segment, constituting the lower pole of the kidney, lies both in an anterior and a posterior plane The posterior segment lies entirely in a posterior plane and occupies an area between the posterior part of the apical segment and the posterior part of the lower segment (Fig 1-65B).

Each of the five segments of the kidney has its own specific blood supply, furnished by a separate vessel variously derived from the renal artery, the aorta, or otherwise. Typically, the anterior division of the renal artery gives rise to the upper, middle, and lower segmental arteries, the apical segmental artery in most cases, likewise, arising from it The posterior division of the renal artery supplies only the posterior segment but, according to Graves, 10 per cent gives off the apical artery The posterior segmental artery, a continuation of the posterior division of the renal artery, after crossing the upper border of the pelvis, courses behind and in close association with the junction of the upper calyx and the pelvis, a landmark which is constant Running under the lip of the hilus, the artery forms a curve, from which branches are given off laterally These comprise three groups, upper (one or two), middle, and terminal Inside the kidney, the lower segmental artery divides into an anterior and a posterior branch, the middle segmental artery has terminals that interdigitate with those of the posterior division The upper segmental artery arises either in the hilus or under the hilar lip and divides intrarenally into two branches.

The apical segmental (superior polar) artery has the most varied sites of origin According to Graves (1956), it arises from the trunk of the anterior division or the upper segmental artery (43 3 per cent), from the junction of the anterior and posterior division of the renal artery (23 3 per cent), from the renal stem or aorta (23 3 per cent), and from the posterior division (10 per cent) In about one-third of specimens, an accessory renal artery, most frequently derived from the posterior division, enters the posterior aspect of the apical segment

Variations in the origin of the other segmental arteries may be classified into three groups. (1) the lower artery arises first from the renal artery anywhere from the aorta to the hilus or separately from the aorta, while the upper and middle segmental arteries have a common origin (53 3 per cent); (2) the lower artery arises with the upper, the middle coming from the lower (16 6 per cent); (3) upper, middle, and lower segmental arteries arise from the same point (16 6 per cent).

Thus, in view of Graves' discovery of the segmental structure of the human kidney, the baffling variational anatomy of the arteries in the renal pedicle, the varieties of terminal branching at or near the hilus, the presence of supernumerary renal arteries (two to four) in the renal pedicle, and the occurrence of superior and inferior polar arteries stemming from the renal artery or the aorta are phases of renal vascularization that are definitely understood and solved Graves emphasizes that by arteriograms, the intrarenal distributions of the renal arteries are identifiable, as there is always a constant pattern, irrespective of the varied origin of the segmental arteries The next point emphasized is that the five segmental arteries to the kidney are readily accessible to the surgeon at operation. They may actually be seen at the hilus, and by temporary compression of the renal vessel, which produces a purplish discolorization of the area supplied, one can readily determine, which specific segment of the kidney the compressed artery supplies.

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occurs rather frequently. The superior or intermediate of the triple renal arteries may supply a superior polar or a suprarenal branch, the inferior may give off the testicular or ovarian artery, or an inferior polar branch. *Quadruple hilar aortic renal arteries* do occur, but reports of them have been few. In the usual quadruple pattern, the four renal arteries arise from the aorta in segmental sequence, their point of origin being from that of the superior mesenteric artery to that of the inferior mesenteric artery (Anson). The upper two renal arteries may have a postcaval course; the lower two, a precaval one. The upper two may pass in front of the pelvis, the lower two behind it. Four renal arteries to the kidney can be effected by a variety of combinations, such as two hilar *and two polar*, three hilar and one polar, three polar and one hilar. The four renal arteries, occasionally, have the same caliber, but more frequently only one of them is large, the others are smaller and are distributed to the upper or *lower extremity* of the kidney.

SUPERIOR POLAR ARTERIES. *They are usually* single and arise separately from the aorta (7 per cent of 11,000 kidneys) or as a branch from the proximal, middle, or distal portion of the renal artery *(12 per cent). They may be double or triple*, unilaterally or bilaterally, with a varied aortic or renal source of origin for each. Often they arise from an inferior suprarenal artery or from its adipose capsular branch to the kidney. In some instances, they arise from the inferior phrenic artery *or from the* superior mesenteric artery. Frequently, *they* give off several branches to the suprarenal gland, a fact to be remembered in removal of *the latter (Fig. 1-63).*

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made on a radial and intersegmental plane, the area may prove to be less vascular.

Thus, as with so-called accessory hepatic arteries and ducts, the conclusion has been reached that *aberrant renal arteries are normal renal arteries that have a precocious origin, from the renal artery or the aorta or some other source,* and that severance of any renal artery will produce necrosis in the area it supplies, for inside the kidney there are no collaterals between the five segments, each of which has its own blood supply Multiple (supernumerary) renal arteries no longer offer any difficulty, for while their distribution is constant in the kidney, if the underlying embryology of the vascularization of the kidney is kept in mind their presence may readily be explained. In early embryos (18 mm), as shown by Felix (1912), the mesonephric arteries in the upper lumbar region form a network (the rete arteriosa urogenitale), from which the gonads, the mesonephros, and the definitive kidney (metanephros) are vascularized by segmentally arranged arteries Aberrant renal arteries arising separately from the aorta may be regarded as persistent mesonephric arteries, whereas renal arteries having a proximal origin in the renal pedicle or at the hilus may be regarded as variations of degeneration of the primitive segmentally arranged mesonephric arteries, the number of which at one stage of development was as high as 20 (Broman). The classical illustration of Felix on a reconstruction of the mesonephric arteries can be found in Merklin and Michels (1958)

Blood Supply of the Pelvis, Calices, and Ureter. Anatomic knowledge of the diverse vascularization patterns of the cited structures is meager, yet important clinically and surgically (Michaels, 1948, Daniel and Shackman, 1950; Douville and Hollinshead, 1955) According to the latter authors, the vascular network of the renal pelvis is markedly different from that of the ureter, being formed by anastomosing branches of several stem arteries derived from the renal artery at different levels Communications between the arteries are so numerous that dangerous surgical interference with the blood supply to the pelvis seems unlikely

As to the blood supply of the ureter itself, Fitel (1895) was among the first to state that the arteries to the upper part of the ureter comprised derivates from the renal, aorta, common iliac, and hypogastric arteries and reached the ureter on its medial side, whereas the arteries supplying the distal part of the ureter were derived from the testicular (ovarian), vesical, uterine, and vaginal branches and reached the ureter on its lateral side.

By means of injected specimens, Michaels showed that the ureter receives its main blood supply through long arteries, which arise from the lower end of the aorta, common iliac, and hypogastric arteries. The lower end of the ureter, close to the bladder, is commonly supplied by an artery derived from the vesicodeferential branch of the hypogastric artery or from the inferior vesical. Reaching the ureter, the long arteries divide into ascending and descending branches that anastomose with similar branches derived above from the renal and testicular or ovarian arteries, while below they communicate with branches from the uterine, vaginal, superior and inferior vesical arteries, and, occasionally, with the middle hemorrhoidal artery. From the pelvis to the bladder, the long arteries give off secondary branches that ramify around the ureter and anastomose with one another and with upper and lower branches. Tertiary branches given off by the secondary branches pierce the musculature of the ureter. In some instances, the long ureteric arteries are double or even triple.

Daniel and Shackman noted that the ureteric blood supply is seldom symmetric on both sides and that there is a marked variation in subjects, especially for the intermediate section of the ureter, which may take its blood supply from the upper or lower abdominal half of the aorta, from the testicular (ovarian), common iliac, or internal iliac arteries Sources of origin of the long ureteric arteries comprised the following arteries: renal, 98 per cent, upper and midaorta, 18 per cent, ovarian artery, 8 per cent, testicular, 30 per cent, lower aorta, 26 per cent, common iliac, 25 per cent, internal iliac, 15 per cent, uterine, inferior and superior vesical, 98 per cent. Some authors maintain that the ureters may be divided at any point if they have large arteries with large anastomoses, but that when the anastomotic branches are minute, they can be divided only at or above the vascular anastomosis

Excellent illustrations of the blood supply to the ureter can be found in the atlases of Grant and of Anson

The Gonadal (Testicular or Ovarian) Arteries. Variations in the origin and course of

the gonadal arteries have been described by many authors

Testicular or ovarian arteries (there is no sexual difference of origin) predominantly arise from the anterior surface of the aorta below the renal vein, less commonly behind or above the latter In about 15 per cent of cases, they arise from the renal artery, one of its branches, or an accessory renal artery. Occasionally, they may arise from a suprarenal, phrenic, superior mesenteric, lumbar, common iliac, or hypogastric artery. In many instances (17 per cent), the gonadal arteries are double on one side, less frequently on both sides In such cases, both arteries may have either an aortic or a renal origin, or both may be derived from the same source As a rule, the inferior of dual gonads is of aortic origin, the superior being either from the aorta or the renal artery. Occasionally, the gonadal artery arises from the aorta by two or three roots. Level of origin of the gonadal artery varies from L1 to L3 (Adachi).

ARCHED GONADAL ARTERY. Of surgical and clinical importance is the fact that gonadal arteries, by crossing the renal vein, are often (18 per cent) *components of the renal pedicle* In an investigation of 183 dissections, Notkovich classified the gonadal arteries in accord with their relation to the renal vein into three types. Gonadal arteries may *arise from the* aorta or renal artery (1) behind or below the renal vein, (2) above the level of the renal vein, (3) behind or below the renal vein but, instead of descending, the artery on the left ascends behind the renal vein, curves over its upper border (lateral to the suprarenal vein), and then descends in front of it. The latter type (22 per cent) constitutes the well-known *arched testicular artery of Luschka* (1864), so important in urology. The looped course of the testicular (ovarian) artery may be *in front of* the renal vein when the latter passes behind the aorta The unfamiliar relations of gonadal arteries were likewise stressed by Anson and Kurth (1955) and are depicted in Fig 1-64

It is important that the arched gonadal artery may be a pathologic factor in the compression of the renal vein, or a possible etiologic factor in idiopathic varicocele in man, and in ovarian varicocele or varicocele of the broad ligament, in the female The arched variety may, likewise, be a factor in *orthostatic albuminuria* and, by compressing the renal vein, may have a direct influence on the direction of the blood flow from the kidney and gonads (Notkovich, 1956).

Common Iliac Arteries. Predominantly, the right and left common iliac arteries arise as lateral terminal branches of the aorta at the level of the lower third of L4, at times a bit higher or lower depending on the length of the abdominal aorta, which is about 14 cm in the male and 12 cm in the female (Taniguchi). According to Adachi, the average caliber of the common iliac artery is 7 mm, with variations from 6 to 11 mm. The range of their length varies from 10 to 90 mm, with a median value of 30 to 40 mm The statement that the right common iliac artery is invariably longer because bifurcation of the aorta occurs to the left of the midline is false, for the arteries may have the same length (Quain, 1844), or the right may be longer than the left, and vice versa.

In the Japanese, according to Adachi, the left common iliac artery is more often longer than the right. In their respective oblique course lateralward, the common iliac arteries diverge from one another at an angle of 60° in the male and about 65° in the female. A few cases have been observed in which the common iliac arteries were lacking, the external and internal iliac arteries then arising directly from the aorta Adachi observed a case in which the right common iliac was very short, the left being of normal length A rare pattern is the one in which the common iliac arteries are dual, or in which the hypogastric artery is lacking

BRANCHES Aside from its terminals (external iliac, hypogastric) and a few unnamed branches *distributed to* the peritoneum and subperitoneal tissue, and a ureterodeferential branch frequently arising from the common iliac artery as the ureter crosses it, the common iliac artery normally has no branches Aberrantly, it may, in some instances, give rise to a middle or lateral sacral branch, an accessory renal (inferior polar) artery, or a testicular artery or ovarian artery. In a horseshoe or an ectopic pelvic kidney, one (or more) of the renal arteries arises from the common iliac arteries or middle sacral artery Cases have been reported in which one or the other of the common iliac arteries gave rise to an iliolumbar, second or

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9

The pulmonary artery and its branches

EDWARD A. BOYDEN

Anatomically the pulmonary arterial tree is so constructed as to serve two functions It propels nonaerated blood to the respiratory portions of the bronchial tree, and it contributes both tensile and bending strength to the lungs (von Hayek). After leaving the hilus, the subdivisions of each pulmonary artery become closely applied to corresponding branches of the bronchial tree, which in turn are sheathed in cartilage plates for a distance of two-thirds to three-fourths of the way to the periphery (Hayward and Reid). Arteries and bronchi thus provide a framework for the parenchyma The veins, lying between adjacent bronchi, afford only tensile strength.

This general similarity of pattern in the branching of bronchi and arteries is no coincidence but is due to the early investment of the bronchial tree by a vascular network. As the bronchial elements take form, corresponding channels appear in the arterial network (Wells and Boyden). This network also provides opportunities for "cutoffs" in a winding blood stream, and so explains the frequency with which anomalous arteries cross intersegmental planes

Because the arterial tree follows the bronchial pattern, *right and left pulmonary arteries are asymmetric* [illegible]

of arterie[illegible]

ferent in [illegible]

pal arteries supply homologous segments, the same names and numbers can be given to right and left segmental bronchi and arteries. Having learned the names of segments, one has only to learn the varying patterns on the two sides

Figure 1-66 illustrates the gross relations of the pulmonary artery and its branches to the tracheobronchial tree. The view is anterior, with the anteroposterior axis of each lung rotated somewhat lateralwards. Ten segmental bronchi are recognized in the right lung and nine in the left lung[1] They are designated by the symbols B^1 to B^{10}. Each divides into two major trunks, the subsegmental bronchi. The latter are indicated by lower-case letters, *a* and *b* For example, B^1a is the apical ramus, B^1b the anterior ramus, of the first apical segmental bronchus. A^1a and A^1b are the corresponding arterial rami The reason for naming the subdivisions as far as this level of branching is that most variations from the normal pattern are due to a displaced origin of one or more subsegmental bronchi; i e , for some unknown reason, bronchial buds supplying a given segment often grow from atypical sites on the developing bronchial tree. Usually a corresponding artery arises at this site But in addition to this type of variation, arteries to posterior subsegments frequently arise from posterior sites, as is natural for a channel that develops from a plexus Hence the necessity of being familiar with subsegmental structures.

THE PULMONARY TRUNK

The *common stem* of the right and left pulmonary arteries is a short trunk about 4 to 5 cm long and 3 cm in diameter. It arises from

[illegible]

of th[illegible]

that

trunk[illegible] [illegible] international Nomenclature of the Oto-Rhino-Laryngologists reduces the number on the left side still further by omitting the medial basal bronchus, B^7 (For reasons that make this anatomically unacceptable, see Boyden, 1955)

third lumbar, umbilical, obturator, and even the middle colic arteries (Hyrtl).

Senior (1925) published a classic embryologic interpretation of the recorded arterial anomalies of the human pelvis and thigh. For those interested in a more complete knowledge regarding the marked and, at times, amazing variations of the arteries of the pelvis and peritoneum, the reader is referred to a review made by Poynter, excellent descriptions and illustrations by Anson, and the monumental text by Adachi

the fibrous base of the heart anterior to, and to the left of, the ascending aorta *Three semilunar valves* separate the pulmonary trunk from the conus arteriosus of the right ventricle. Just above these are the pulmonary sinuses—corresponding bulges in the pulmonary trunk These lie at a higher level than the corresponding aortic sinuses.

As the pulmonary trunk ascends within the pericardial cavity, it moves posteriorly and somewhat spirally around the left side of the ascending aorta until it reaches the concavity of the aortic arch There it bifurcates into right and left pulmonary arteries The former turns backwards and to the right, beneath the arch of the aorta, at an angle of 60 to 70° to the main trunk, the latter continues posteriorly and *to the left*, at an angle of 45° (von Hayek) but passes in front of the descending aorta

At the concavity of the aortic arch, the serous pericardium is reflected onto the ascending aorta and pulmonary trunk just before the latter divides Consequently, the left pulmonary artery and the *ligamentum arteriosum* (which connects the most proximal segment of the left pulmonary artery with the descending portion of the aortic arch) lie wholly outside the pericardial cavity In contrast to this, *much of the pulmonary trunk and the right pulmonary artery are covered by the serous layer at the upper end of the pericardial cavity, or by its extension, the transverse sinus of the pericardium*

One of the important relations is the hooking of the *left recurrent laryngeal nerve* around the ligamentum arteriosum Passing just anterior to the ligament are the autonomic nerves to the superficial cardiac plexus and the ganglion of Wrisberg.

Attention has already been called to the different direction which right and left pulmonary arteries take as soon as they leave the parent trunk In addition, they differ in size, the right pulmonary artery having an approximate diameter of 24 mm, and the left pulmonary artery, of 20 mm (Fig 1-66).

THE RIGHT PULMONARY ARTERY

Soon after its origin the right pulmonary artery crosses the right primary bronchus between the upper and middle lobe bronchi, then enters the depths of the interlobar fissure to descend on the lateral surface of the lower lobe bronchus. By crossing the main stem below the upper lobe bronchus, it makes the latter "eparterial." By contrast, all the bronchi of the left lung are "hyparterial," except in rare anomalies. Impressed by this seemingly dominant role of the arteries, Aeby assumed that the left lung had "lost" its eparterial bronchus. Therefore, the left upper lobe could only be homologous with the right middle lobe. (For history of earlier views, see Boyden, 1955)

The Truncus Anterior. As the pulmonary artery crosses the right main bronchus, it gives off its first (and largest) branch, the *truncus anterior* (Fig 1-66). Primarily this supplies segments on the mediastinal surface of the upper lobe, but in 88 per cent of the lungs (Boyden and Scannell) it also carries a recurrent artery to the posterior segment—especially to its apical portion, A^3a (Fig 1-66). This truncus anterior exhibits three modes of branching. Typically, it bifurcates into superior and inferior divisions (68 per cent). The former supplies the apical segment (B^1) and usually the apical ramus of the posterior segment (B^3a); the latter supplies the anterior segment (B^2). A variant type (18 per cent) may be described as trifurcate. In this pattern, the middle limb consists chiefly of recurrent branches to subsegments on the interlobar surface of the upper lobe. The third type (14 per cent) is a double truncus anterior arising as two separate stems from the main artery. Both these stems pass anterior to the anterior segmental bronchus (B^2). The inferior of the two anterior trunks should not be confused with ascending arteries (viz , A^3b, Fig. 1-66) which pass posterior to B^2.

The Pars Interlobaris. After giving off the truncus anterior, the right pulmonary artery passes into the depths of the fissures which separate the upper from the middle and lower lobes. Hence this portion of the artery has been designated as the *pars interlobaris* (Boyden, 1945). It gives rise to three sets of arteries, which will be discussed separately, although they may overlap each other in certain patterns. These are "ascending" arteries to the posterior and anterior segments of the upper lobe, middle lobe arteries, and arteries to the superior segment of the right lower lobe

"ASCENDING" UPPER LOBE ARTERIES The useful distinction between arteries which "run back" from the anterior side of the hilus to

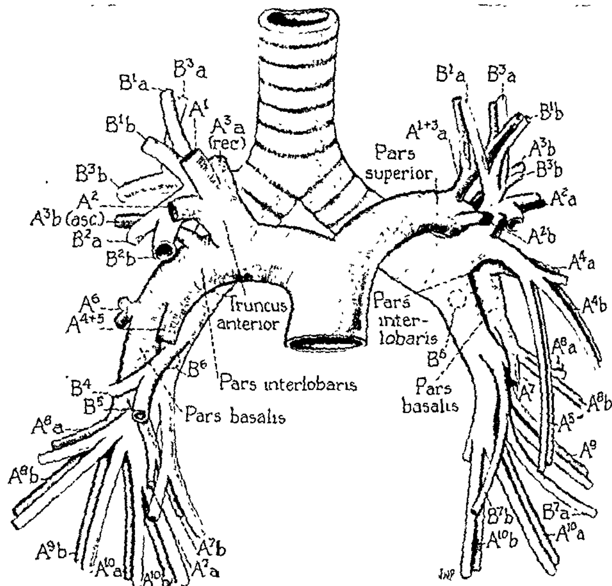


Fig. 1-66 Anterior view of tracheobronchial tree and associated pulmonary arteries. The segmental bronchi, *B*, and corresponding arteries, *A*, are numbered from 1 to 10. Lower-case letters *a* and *b* indicate subsegmental branches. Corresponding bronchi and arteries have the same name.

Right upper lobe
- A^1—*Apical seg. art.*
  - A^1a—apical ramus
  - A^1b—anterior ramus
- A^2—*Anterior seg. art.**
  - A^2a—posterior ramus
  - A^2b—anterior ramus
- A^3—*Posterior seg. art.**
  - A^3a—apical ramus
  - A^3b—posterior ramus

Middle lobe
- A^4—*Lateral seg. art.*
- A^5—*Medial seg. art.*

Right lower lobe
- A^6—*Superior seg. art.*
- A^7—*Medial basal seg. art.*
  - A^7a—anterior ramus
  - A^7b—medial ramus
- A^8—*Anterior basal seg. art.*
  - A^8a—lateral ramus
  - A^8b—basal ramus
- A^9—*Lateral basal seg. art.*
  - A^9a—lateral ramus
  - A^9b—basal ramus
- A^{10}—*Posterior basal seg. art.*
  - $A^{10}a$—laterobasal ramus
  - $A^{10}b$—mediobasal ramus

Left upper lobe
- A^{1+3}—*Apical-posterior seg. art.**
  - A^1—apical ramus
  - A^3—posterior ramus
- A^2—*Anterior seg. art.**
  - A^2a—lateral ramus
  - A^2b—anterior ramus
- A^4—*Superior lingular seg. art.*
  - A^4a—lateral ramus
  - A^4b—anterior ramus
- A^5—*Inferior lingular seg. art.*

* In the international terminology of the otorhinolaryngologists, Arabic numbers are interchanged (*viz.*, the anterior segment is B^3, the posterior segment B^2).

lyzed by Boyden and Hartmann, the mean number was 5.4 per left upper lobe.

The Pars Superior. ARTERIES ORIGINATING ANTERIORLY The only artery that arises consistently from the anterior aspect of the pars superior is A^2b, the ramus supplying the anterior subsegment of the anterior segment It may also carry A^2a, the branch to the lateral subsegment (18 per cent), or it may be double, or it may be associated at its origin with one of the two following arteries

A second artery that may arise at this site (38 per cent) is A^1, the artery to the apical segment.

A third artery that may arise at this site (22 per cent) is an artery to one or both lingular segments (A^4, A^5) (In a more recent study comprising 100 specimens (Boyden, 1955) the number rose to 30 per cent) This is usually concealed, passing in front of the upper lobe bronchus but beneath the superior pulmonary vein

ARTERIES ORIGINATING SUPERIORLY These comprise those arteries to the apical-posterior segment which do not arise anteriorly. They are represented by two or more separate stems in 78 per cent of specimens This is unexpected in view of the fact that the corresponding subsegmental bronchi (B^1, B^3) always arise from a common stem. In most cases they originate superiorly, but they tend to spread over the arched portion of the left pulmonary artery and so may wander onto the upper portion of the pars interlobaris Thus is especially true of A^3b (Fig 1-66), the artery to the interlobar portion of the posterior subsegment Equally important is the fact that this artery arises separately in 42 per cent of specimens Being hidden under the apex of the lung, it is sometimes overlooked in surgery until it hemorrhages

The Pars Interlobaris. This is the portion of the left pulmonary artery which lies in the depths of the interlobar fissure. It gives rise to a varying number of arteries, depending upon whether one, or both, of the lingular arteries arises anteriorly, or whether the artery to the superior segment of the lower lobe is represented by a single vessel or multiple stem

Frequently, arteries to the apical-posterior segment are found at its extreme upper end (as A^3b in Fig. 1-66), arteries to the lingular segments (A^4, A^5) at its lower end, and the artery to the superior segment (A^6) somewhere in between—along the outer curvature of the pars interlobaris. (In Fig. 1-66 this is hidden by intervening structures.) A^2a, the artery to the lateral portion of the anterior segment (Fig. 1-66), is frequently absent from this region, either because it arises anteriorly with A^2b (18 per cent), or because its corresponding bronchus is absent (35 per cent of 100 specimens). When present, it frequently arises in conjunction with the lingular arteries (18 per cent).

ARTERIES TO THE SUPERIOR SEGMENT (A^6). These arteries merit special consideration because in 36 per cent of specimens there are two, and sometimes three, of them (Pitel and Boyden). Multiple arteries to the apical portion of the lower lobe are thus twice as common on the left side as on the right. Curiously enough, the lowest of these arises from the posterior basal artery (A^{10}) in 12 per cent of cases. When A^6 is represented by a single artery, it usually lies at or above the level of the lingular arteries. For this reason, in a left lower lobectomy, it is necessary to ligate the superior and the basal arteries separately.

The Pars Basalis. After the lingular arteries are given off, the main left pulmonary artery continues for a varying distance as the pars basalis (Fig 1-66) Almost immediately it enters the hilus of the lower lobe, on the lateral side of the lower lobe bronchus, where it is distributed to the basal segments of the lobe. Its mode of termination is more complicated than on the right side, partly because the corresponding basal bronchus has two principal patterns of branching. In 62 per cent of 110 specimens (Table 28, Boyden, 1955), it bifurcates into B^{7+8} and B^{9+10}, in another 21 per cent it trifurcates into B^{7+8}, B^9, and B^{10}. (In the remaining 17 per cent its patterns are bizarre) Even so, it was unexpected to find that the corresponding artery terminates in A^{7+8} and A^{9+10} in only 42 per cent of specimens In a larger number (46 per cent) it bifurcates into A^{10} and a common trunk for A^{7-9} As a consequence of this clustering together of arteries to the first three basal segments, the artery to the lateral basal segment (A^9) develops as a hidden branch of A^7, A^8a, or A^8b in 22 per cent of cases Thus, in segmental resections of the anteromedial basal segments the artery to the

supply the posterior segment and those that "ascend" to the under side of the upper lobe from the pars interlobaris is credited to the late English anatomist Appleton. It is of practical importance because it teaches the surgeon that in right upper lobectomies, he must search both sides of the lobe for arteries. The truncus anterior is always present, but in about 90 per cent of cases, there are also from one to three ascending arteries. Those to the posterior segment (of which the majority supply $B^{3}b$) are about twice as numerous as those to the anterior segment (Table 2, Boyden, 1955).

Before leaving discussion of the upper lobe, it should be noted that the anterior segment is the most easily resectable of the three, but even so, arteries not infrequently cross its intersegmental planes. In fact, if all arteries to the segment were ligated, some of the blood supply to adjacent segments would be interrupted in about a third of the patients

THE ARTERIES TO THE MIDDLE LOBE. These arise from the inner curvature of the pars interlobaris (Fig. 1-66) In approximately half the cases there may be two separate arteries instead of one; rarely there may be three. In the latter event, the lowest arises as an aberrant branch of the medial basal or anterior basal artery, A^{7} or A^{7+8} (Table 2, Boyden and Hamre).

The spacing of these arteries is also of practical importance. If the interval between the lowest upper lobe artery and the highest middle lobe artery is sufficient to permit ligation of the main artery, then a bilobectomy of middle and lower lobes is possible (Lindskog et al.). In the author's 50 specimens such a free "intermediate" segment occurred in less than half the cases.

A third point of clinical interest is the fact that arteries to the middle lobe fail to reproduce the bronchial pattern in 46 per cent of cases Because these arteries cross intersegmental planes so frequently, and because medial and lateral segments are not large, a lobectomy is generally preferred to a resection of one segment.

ARTERIES TO THE SUPERIOR SEGMENT (A^{6}) Typically, one such artery should arise at the lower end of the pars interlobaris (Fig. 1-66) at, or just below, the level of the middle lobe artery (or in a similar relation to the second middle lobe artery, if there are two). However, in a fifth of the cases the superior segment is supplied by two (or even three) separate arteries. If this condition is complicated by the presence of "ascending" arteries or multiple middle lobe arteries, the pars interlobaris may exhibit as many as five arteries to adjacent segments or subsegments (cf. Figs 49 and 82, Boyden, 1955).

The Pars Basalis. After the artery to the superior segment is given off, the main portion of the right pulmonary artery continues for a varying distance as the pars basalis However, it soon enters the hilus of the lower lobe, on the lateral side of the bronchus, there to branch into the arteries that supply the basal segments. In the prevailing pattern (44 per cent of specimens, Ferry and Boyden), it may be said to terminate by dividing into lateral basal and posterior basal arteries (A^{9}, A^{10}). Meanwhile it has given off one or more branches to the subsuperior zone and to medial basal and anterior basal segments (respectively, A^{*}, A^{7}, A^{8}). To a large degree the arborization of arteries (and bronchi) seems to be determined by the pattern of the medial basal bronchus (B^{7}). In 56 per cent (of 50 specimens) it divides normally, as in Fig. 1-66. In another 24 per cent it arises more medially to fork around the common basal vein. In the remaining 20 per cent it is absent, as such, but its two rami ($B^{7}a$, $B^{7}b$) arise as displaced branches from bronchi of adjacent segments (Ferry and Boyden). In the last two types, $A^{7}b$ arises posteriorly and medially, and the pattern of branching is otherwise disturbed. Particularly variable are the arteries to the anterior basal segment (A^{8}).

THE LEFT PULMONARY ARTERY

As one compares left and right pulmonary arteries, the most striking difference is the absence of a typical truncus anterior on the left side (Fig 1-66) Usually it is replaced by a group of one or more smaller arteries, arising from the anterior or superior aspect of the left pulmonary artery or from both Only in 18 per cent of lungs are they combined into a trunk long enough to be ligated (Boyden and Hartmann). Therefore, in a left upper lobectomy, it is necessary for the surgeon to ligate separately from four to seven upper lobe arteries (Kent and Blades). In the 50 specimens ana-

lyzed by Boyden and Hartmann, the mean number was 5 4 per left upper lobe.

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lateral basal segment could be unwittingly removed with the arteries to the resected segments.

It is not within the province of this section to discuss the anastomoses between pulmonary arteries and bronchial arteries, and between pulmonary arteries and veins, the minute peripheral branch of the pulmonary artery, or the occurrence of accessory pulmonary arteries arising from such systemic vessels as the aorta. References to the last two subjects may be found in von Hayek's text and in Boyden (1955).

10

The azygos and the lumbar system of veins

BARRY J. ANSON

The vessels of the azygos and lumbar systems constitute together a schema of parietal vascular drainage in which transversely coursing veins, generally segmental, terminate in longitudinal veins, which more often than not are continuous at the abdominothoracic level (Fig. 1-67A and B). This is tantamount to stating that the arbitrary division into azygos and lumbar systems is defensible solely for purposes of convenient description, the concept of segregation of the two parts (superior and inferior to the respiratory diaphragm) finding no support in either structure or function

Following the customary method of presentation, the anatomy of the azygos system of veins will be considered first and independently of the lumbar, then the latter system will be described, together with the roots which bring the two systems into continuity.

AZYGOS SYSTEM OF VEINS

General Features. The azygos vein usually *begins opposite the* first or second lumbar vertebra in a tributary which is a continuation of the ascending lumbar vein *Sometimes, however*, the communication is a branch of a renal vein or of the *inferior* vena cava

The azygos vein *enters the thorax* through the aortic hiatus *in the diaphragm, and ascends* along the right side of the vertebral column, typically to the level of the *fourth thoracic* vertebra; here it ordinarily arches forward over the root of the right lung, and terminates in the superior vena cava, *just proximal* to the point at which that vessel passes through the pericardium. In its thoracic course, the azygos vein lies upon the intercostal arteries, to the right of the aorta and the thoracic duct, and is partly covered by the pleura

The azygos vein receives the *right subcostal* and *intercostal veins*, the upper three or four of the latter vessels opening by a common stem, termed the *highest superior intercostal vein*. It receives the *hemiazygos veins* and tributaries from the esophagus, mediastinum, pericardium, and bronchi

The intercostal veins on the left side, below the upper three intercostal spaces, usually form two trunks, named the hemiazygos and *accessory hemiazygos veins*

The hemiazygos vein is, in many instances, a continuation of the left ascending lumbar or left renal vein (see below) It enters the thorax through the left crus of the diaphragm, *then*, ascending in paravertebral course on the left side, *in* typical cases as high as the ninth thoracic vertebra, the vein passes across the vertebral column, behind the aorta, esophagus, *and thoracic* duct, to end in the azygos vein. The hemiazygos vein is described as receiving the lower four or five intercostal veins and the subcostal vein *of the* left side, and a varying number of esophageal and mediastinal tributaries

The accessory hemiazygos vein descends on the left side of the vertebral column, *receiving* as tributaries *veins from* the three or four intercostal spaces which intervene between the

highest left intercostal vein and highest tributary of the hemiazygos vein. Familiar descriptions in standard textbooks recognize that the accessory hemiazygos vein is likely to cross the midline at the level of the body of the eighth thoracic vertebra to join the azygos vein It is further recognized that the vessel may end in the hemiazygos vein

Variations. It is not the purpose of the present chapter to discuss the developmental anatomy of the azygos and ascending lumbar veins; these parietal vessels, with their phrenic and caval communications and their visceral connections (direct and indirect from pelvic to cervical level), are associated parts of an extensive venous pattern laid down embryologically in 10 longitudinal venous trunks and an even more complex series of transverse channels. Segments of this many-sided pattern are retained or obliterated in such a way as to produce a simpler arrangement, although still multiform, for the adult body (Seib, 1934).

Because the aim of this treatise is avowedly practical, only "terminal" patterns will be con-

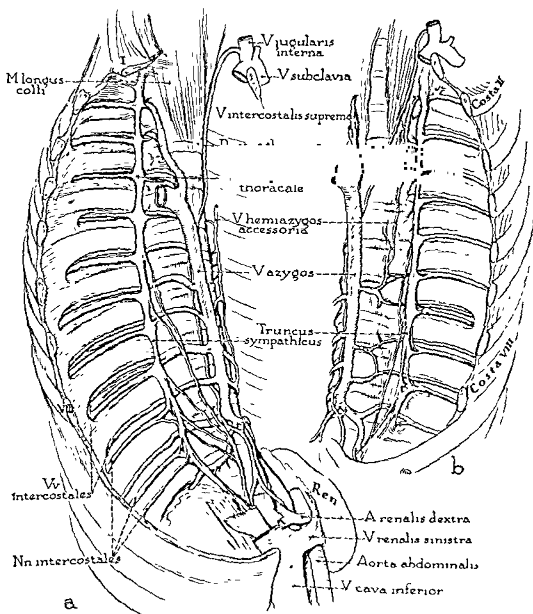


Fig. 1-67A. Azygos system of veins, the intercostal tributaries with the corresponding arteries and nerves, the thoracic duct, and the sympathetic trunk a and b, Right and left sides, respectively, of the same dissected specimen. Removal of the respiratory diaphragm permits exposure of veins which, at or near renal level, bring the lumbar system of veins into continuity with channels of the azygos system.

sidered in discussion of the azygos and the lumbar divisions of the composite system

From the examination of the thoracic portion of the azygos venous system in 200 cadavers, it was found that the azygos vein itself is relatively constant in arrangement, usually it arises at the level of the twelfth thoracic vertebra, from one, two, or even three roots of origin, receives all the right intercostal veins, except the first, as it passes cranialward to empty into the superior vena cava (Seib). The second, third, and fourth veins usually unite to form a common trunk, the *right superior intercostal vein*, which ends in the azygos arch

The hemiazygos veins in the same specimens were inconstant, although fundamentally part of a single longitudinal trunk which arises at the thoracic level of origin of the azygos, by a single vein or by confluent vessels, the longitudinal vein is broken into segments which receive intercostal veins from different portions of the left thoracic wall. On the basis of discontinuity in scheme of reception of tributaries, the segments are named hemiazygos, accessory

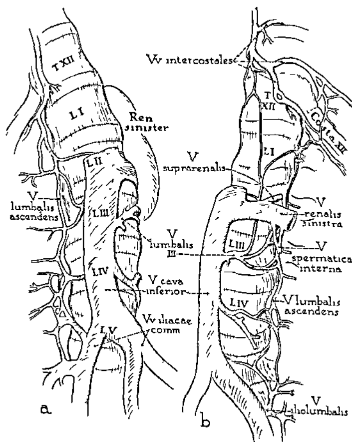


Fig 1-67B. Ascending lumbar veins, their segmentally arranged lumbar tributaries, and communications with caval and azygos veins *a* and *b*, Right and left sides, respectively, of the same dissected specimen The thoracic portion of the dissection is *shown in (A)*. *a*, Demonstrating the paravertebral *course* of the ascending lumbar veins, communications with the inferior vena cava at three vertebral levels, connection with the common iliac veins caudally, and continuity with the azygos vein cranially *b*, Showing comparable *course*, *tributaries*, and communications with the right side *The* iliac connection takes place through a common trunk with the iliolumbar vein; the second lumbar vein communicates with the renal vein (by *which it* is here concealed), the third lumbar vein (in *the form* of a lumboazygos trunk) divides to send one branch to the azygos vein [see (A)], the other to the ascending lumbar vein and the lowest intercostal vein Plexiform arrangements occur on both sides, as do venous loops around either the intercostal or the lumbar arteries or nerves (*From Anson. Atlas of Human Anatomy. Saunders, 1950*).

hemiazygos, and left superior intercostal vein. In 25 per cent of cases the single trunk empties into the left innominate vein by way of the left superior intercostal vein.

Altogether, 21 different arrangements are recognized in Seib's series (Fig. 1-68A). Despite such diversification, all the patterns are *reducible to three main categories, viz.*, double-column, single-column, and transitional (Fig. 1-68B).

LUMBAR SYSTEM OF VEINS

General Features. The lumbar veins, typically described as four in number on each side, receive the blood by dorsal tributaries from the muscles and integument of the loins, and by tributaries from the abdominal wall, where they communicate with the epigastric veins. At the vertebral column, they receive veins from the vertebral plexuses and then pass forward, around the sides of the vertebral bodies beneath, or in the substance of, the psoas major muscle They terminate on the dorsal surface of the inferior cava The left lumbar veins are longer than the right, since they must take a *retroaortic* course to reach the inferior vena cava (Fig 1-71).

The lumbar veins are interconnected by a *longitudinal vessel* which passes in front of the transverse processes of the lumbar vertebrae, and which is called the *ascending lumbar vein;* it is described as forming the most frequent origin of the corresponding azygos or hemiazygos vein, and as serving to connect the common iliac and iliolumbar veins with the azygos or hemiazygos vein of its own side of the body.[1]

[1] Closely related to veins, and, therefore, *topographically* important, are the *lumbar arteries* They are in series with the intercostal arteries, *are usually* four in number on either side, and arise from the dorsum of the aorta opposite the bodies of the upper four lumbar vertebrae Occasionally a fifth pair, small in size, is present, these arteries arise from [illegible] processes, they enter the musculature of the abdominal wall The arteries of the right side pass behind the inferior vena cava; those of both sides pass beneath the tendinous arches which give origin to the psoas major, and are then continued behind this muscle and the lumbar plexus Crossing the quadratus lumborum muscle, they next pierce the posterior aponeurosis of the transversus abdominis and are carried forward between this muscle and the obliquus internus They anastomose with the following arteries lower intercostal, subcostal, iliolumbar, deep iliac circumflex, and inferior epigastric arteries.

In the interval between the adjacent transverse processes, each lumbar artery gives off a posterior *ramus* which is distributed to the muscles and skin of the back, each such artery furnishes a spinal *branch* which enters the vertebral canal and supplies the spinal cord, meninges, and related structures. *Muscular branches* are supplied from each lumbar artery and from its posterior ramus to the neighboring muscles.

Variations. The conventional descriptions of the lumbar subdivision of the lumboazygos system of veins give little notion of the number of ways in which the pattern may depart from the anatomic "normal." These departures are encountered in both the parietal and the visceral sets of tributaries; those of the former group suggest the type of variation presented by the azygos system; the latter, related to the kidneys and suprarenal glands, are far more complex and numerous than are the bronchial and esophageal tributaries to the azygos vein.

At the phrenic level, in the area of Seib's "lumbar portion of the azygos system," 20 different types of venous pattern are known to occur. They are classified on the basis of arrangement of the intermediate and medial azygos and hemiazygos roots of origin.

At the renal level the occurrence of connections between the several lumbar roots of the azygos is rendered further complex by the presence of communications with the inferior caval system of veins and with the ascending lumbar vein of the left side (Seib). (Here again, the reader will find in Seib's discussion of embryonic sources an impressive account of the varied venous schemata which may occur in the adult body as a result of unpredictable retention or abandonment of channels primordially contributory to a series of longitudinal and transverse vessels)

As already mentioned, consideration of the numerous variations in the venous pattern at vertebral levels from pelvis through thorax involves description of the visceral connections, as well as the parietal Chief among the structures concerned are the *kidneys* and the *suprarenal glands* The simple form of renal pedicle

commonly portrayed in standard texts cannot be accepted in the light of critical study of the kidney area.

The renal vascular elements are not isolated from the blood vessels of neighboring regions; instead, the kidneys receive numerous arteries from several sources, and venous tributaries converge upon them from adjacent and even from remote visceral and parietal structures, thereby providing a remarkable complexity of pattern and vascular interrelationships. The fallacy of the concept of the renal pedicle is heightened by a consideration of the combined renal and suprarenal arterial supply Together, these sets of vessels often cover a quadrilateral vascular field whose vertical dimension may exceed that of the kidney itself. *Supernumerary renal vessels* of large size are common, being derived from the aorta as serially arranged stems Smaller ones to the hilus or to the renal parenchyma (that is, extrahilar rami) are commonly branches of arterial stems which are also suprarenal *Supernumerary renal arteries*, large and small, are also derived from the internal spermatic and superior mesenteric arteries, additionally, when the kidneys are ectopic or fused, they *may* arise from the iliac, hypogastric, and middle sacral arteries

Striking dissimilarity exists between the *suprarenal veins* of the two sides—or, rather, similarity is limited to the *occurrence, on each* side, of a single venous channel On the left side the suprarenal vein enters the renal vein, as a channel of a vertical course, usually confluent with the phrenic vein (Fig 1-69A, *c–e*) On the right side the suprarenal vein is much shorter, independent of other neighboring vessels ...

... bears little resemblance to that of the left In its relatively short course from the kidney to the inferior vena cava, the right renal vein rarely *receives* a tributary (Fig 1-69B, c) When a venous channel does enter the renal, it is the gonadal vein (spermatic or ovarian), not —except when the aorta and vena cava are transposed—the lumbar or the suprarenal The longer left renal vein, on the contrary, regularly receives the following tributaries suprarenal and inferior phrenic veins, from above, frequently by a common, or confluent channel (Fig. 1-69B, *c* and *e*); and the spermatic (or ovarian) and second or third lumbar veins from below, likewise often by a confluent vessel (Fig 1-69B, *c*). Reception of these tributaries is a result of passage of the left renal vein across territory occupied by the left suprarenal gland, primordially by the testis or ovary, and by lumbar veins, which, on the opposite side, drain directly into the inferior vena cava In the preponderant number of specimens there is a single renal vein on the right side. However, sometimes there are two, or even three, veins (Fig 1-69B, *b*). When present in duplicate or triplicate, the veins are approximately equal in caliber and parallel in course, rarely do adjacent channels anastomose.

Predictably, on the basis of its posterior relationships, the left renal vein is found to be complex, not only in respect to arrangement of its tributary system, but also in regard to its pattern of division and anastomosis. Thus, while the term "pedicle," is somewhat appropriate for the set of blood vessels which enter and leave the right kidney, it is *rarely suitable* for the congeries of channels on the left side. In many specimens, on the left side, in preaortic position, the veins from the kidneys, *which* are constituents of the so-called renal pedicle, may seem to be relatively simple in arrangement, i.e , on each side there is likely to be a single renal vein in front of the aorta (Fig 1-69A, *c*, *d*). However, on the retroaortic, or prevertebral, level, complexity in venous pattern occurs, the retroaortic members of the plexus regularly communicate with lumbar veins, and the retroaortic set of veins is often associated with the deeper division of circumaortic venous ring (Figs 1-69A, *a*, 1-70A, *a*, 1-70B, *a*) The preaortic vein then receives the suprarenal vein, while the retroaortic veins communicate with veins draining the prevertebral connective tissue, and with lumbar *veins* (*Figs*. 1-69B, *a*, 1-70B, *a* and *b*). Usually the retroaortic element of the ring is oblique, *joining* the left renal vein near the hilus of the kidney (Figs. 1-69B, *a*, 1-70B, *a*). However, in rare instances the tributary is *transverse* and enters the parenchyma of the lower pole of the kidney Here it is likely to *receive* iliac and lumbar veins before reaching the inferior vena cava

The direct lumbar tributary of the left renal

hemiazygos, and left superior intercostal vein. In 25 per cent of cases the single trunk empties into the left innominate vein by way of the left superior intercostal vein

Altogether, 21 different arrangements are recognized in Seib's series (Fig. 1-68A). Despite such diversification, all the patterns are reducible to three main categories, viz., double-column, single-column, and transitional (Fig 1-68B).

LUMBAR SYSTEM OF VEINS

General Features. The lumbar veins, typically described as four in number on each side, receive the blood by dorsal tributaries from the muscles and integument of the loins, and by tributaries from the abdominal wall, where they communicate with the epigastric veins At the vertebral column, they receive veins from the vertebral plexuses and then pass forward, around the sides of the vertebral bodies beneath, or in the substance of, the psoas major muscle. They terminate on the dorsal surface of the inferior cava The left lumbar veins are longer than the right, since they must take a retroaortic course to reach the inferior vena cava (Fig. 1-71)

The lumbar veins are interconnected by a longitudinal vessel which passes in front of the transverse processes of the lumbar vertebrae, and which is called the *ascending lumbar vein*, it is described as forming the most frequent origin of the corresponding azygos or hemiazygos vein, and as serving to connect the common iliac and iliolumbar veins with the azygos or hemiazygos vein of its own side of the body.[1]

Variations. The conventional descriptions of the lumbar subdivision of the lumboazygos system of veins give little notion of the number of ways in which the pattern may depart from the anatomic "normal" These departures are encountered in both the parietal and the visceral sets of tributaries; those of the former group suggest the type of variation presented by the azygos system; the latter, related to the kidneys and suprarenal glands, are far more complex and numerous than are the bronchial and esophageal tributaries to the azygos vein

At the phrenic level, in the area of Seib's "lumbar portion of the azygos system," 20 different types of venous pattern are known to occur. They are classified on the basis of arrangement of the intermediate and medial azygos and hemiazygos roots of origin.

At the renal level the occurrence of connections between the several lumbar roots of the azygos is rendered further complex by the presence of communications with the inferior caval system of veins and with the ascending lumbar vein of the left side (Seib). (Here again, the reader will find in Seib's discussion of embryonic sources an impressive account of the varied venous schemata which may occur in the adult body as a result of unpredictable retention or abandonment of channels primordially contributory to a series of longitudinal and transverse vessels)

As already mentioned, consideration of the numerous variations in the venous pattern at vertebral levels from pelvis through thorax involves description of the visceral connections, as well as the parietal Chief among the structures concerned are the *kidneys* and the *suprarenal glands*. The simple form of renal pedicle

[1] Closely related to veins, and, therefore, topo- [illegible] dorsum of the aorta opposite the bodies of the upper four lumbar vertebrae. Occasionally a fifth pair, small in size, is present, these arteries arise from the middle sacral vertebra. The lumbar arteries run in a dorsolateral direction on the bodies of the lumbar vertebrae, behind the sympathetic trunk, reaching the intervals between the adjacent transverse processes, they enter the musculature of the abdominal wall The arteries of the right side pass behind the inferior vena cava, those of both sides pass beneath the tendinous arches which give origin to the psoas major, and are then continued behind this muscle and the lumbar plexus. Crossing the quadratus lumborum muscle, they next pierce the posterior aponeurosis of the transversus abdominis and are carried forward between this muscle and the obliquus internus They anastomose with the following arteries lower intercostal, subcostal, iliolumbar, deep iliac circumflex, and inferior epigastric arteries.

In the interval between the adjacent transverse processes, each lumbar artery gives off a posterior ramus which is distributed to the muscles and skin of the back, each such artery furnishes a spinal branch which enters the vertebral canal and supplies the spinal cord, meninges, and related structures Muscular branches are supplied from each lumbar artery and from its posterior ramus to the neighboring muscles.

channels. The cranial set of capsular veins often receives muscular tributaries (from diaphragm, psoas major, quadratus lumborum), as well as lower suprarenal and phrenic tributaries, before emptying by multiple veins into the renal vein; the inferior set may receive one or more lumbar veins, usually indirectly, a caudal portion of the capsular system frequently joins the genital vein before entering the renal vein.

Dorsal parietal veins of the ascending lumbar system emerge through the quadratus muscle to enter the renal vein (Figs. 1-70A, *a–c*; 1-70B, *a and b*), dissections reveal that this site is also the point at which the vein is the recipient of tributaries from the vertebrae, meninges, and spinal cord In this way the axial musculature, skeletal elements, and central nervous system are brought into direct venous connection with the kidneys.

Vascular complexity, common in the left renal area, is sometimes increased by the occurrence of a *left inferior vena cava* in association with a *circumaortic venous ring* (Fig 1-70B, *a* and *b*). Two *caval channels* then exist side by side, brought into communication cranially by the postaortic element of the *venous ring*, and caudally by the left common iliac vein A third vertical channel is commonly present, in the form of an ascending lumbar vein en route to the hemiazygos vein

It is perhaps important to record that in the author's laboratory a *left inferior vena cava* has been encountered in approximately 3 per cent of a rather large series of specimens. Other authors have recorded a similar percentage occurrence. The *left caval vein* may be as large as the regular vessel of the right side, smaller, or, in rare instances, larger [Fig 1-71(1)]

Fig. 1-68B. *Azygos venous patterns; the most frequent arrangement in each of the* [illegible] *patterns Schematized Abbreviations* [illegible] *and left superior intercostal veins* [illegible] *and left highest intercostal veins,* [illegible] *per cent C, Single-column pattern, 5 per cent.* *(From Seib Am J. Phys Anthr. 1934.)*

vein is typically a single trunk, which traverses a short distance between the point at which it emerges from the psoas muscle and that at which it meets the vein from the kidney, occasionally doubling of the lumbar tributary occurs. The scheme of lumbar drainage varies widely, but there is a tendency toward concentration of the tributaries toward the upper lumbar (that is, renal) level.

Variations are expressed in the following patterns. a single lumbar vein, either the first or second, enters the renal vein, the first and second lumbar veins enter the renal vein separately or by a common trunk, the first or second lumbar vein *first joins a hemiazygos tributary (of lumbar origin) proximal to the point at which they empty into the renal vein, the second or third lumbar veins (one or both independently, or by a common trunk) join the genital (spermatic or ovarian) vein before terminating in the renal vein; a series of lumbar venous tributaries joins a long vertical trunk, the persistent left inferior vena cava, before entering the renal vein.*

In addition, on the left side, the channels of the capsular network often form a *circumrenal venous network*, whose constituents drain directly or indirectly into the renal veins (Fig. 1-70A, *a*). These are not simply retroperitoneal

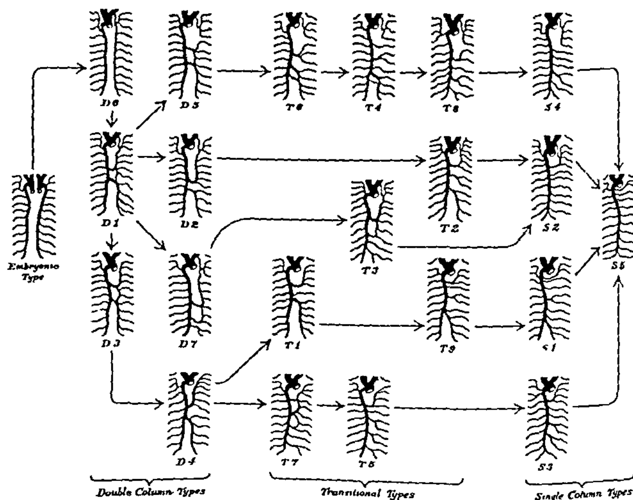


Fig. 1-68A. Patterns in the thoracic portion of the azygos system of veins. Diagrammatic presentation of 21 different types in three major groups encountered in 200 cadavers. Types arranged in structural series, in the order indicated by the arrows. In the double-column group, D, right and left longitudinal veins occur, both unbroken; in the transitional types, T, two, three, or four breaks occur in the left longitudinal vein, in the single-column types, S, five or more breaks occur in the left longitudinal vein (hemiazygos), the unbroken right vein (azygos) receiving most of the left intercostal veins directly. The numerical distribution is as follows in the double-column group of types D1, 49, D2, 25, D3, 25; D4, 11; D5, 3; D6, 2; D7, 1. In the transition group, these are the totals T1, 22; T2, 20, T3, 13; T4, 5; T5, 5; T6, 4, T7, 2; T8, 2; T9, 1 The distribution in the double-column is among five types· S1, 3, S2, 2; S3, 2, S4, 1, S5, 1.

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Fig 1-68B. Azygos venous patterns; the most frequent arrangement [illegible] patterns. Schematized. Abbrev[illegible] hemiazygos vein, AoH, aor[illegible] origin of the azygo[illegible] left renal vein, RAA [illegible] RSIC, LSIC, right a[illegible] intercostal veins; medial roots of orig[illegible] [illegible], LRH, IRH, MRH, lateral, intermediate, and medial roots of origin of the hemiazygos vein, Th 6, the sixth intercostal vein. A, Double-column pattern, 58 per cent of 200 specimens. B, Transitional, 37 per cent. C, Single-column pattern; 5 per cent. (From Seib. Am J. Phys Anthr, 1934)

vein is typically a single trunk, which traverses a short distance between the point at which it emerges from the psoas muscle and that at which it meets the vein from the kidney; occasionally doubling of the lumbar tributary occurs. The scheme of lumbar drainage varies widely, but there is a tendency toward concentration of the tributaries toward the upper lumbar (that is, renal) level.

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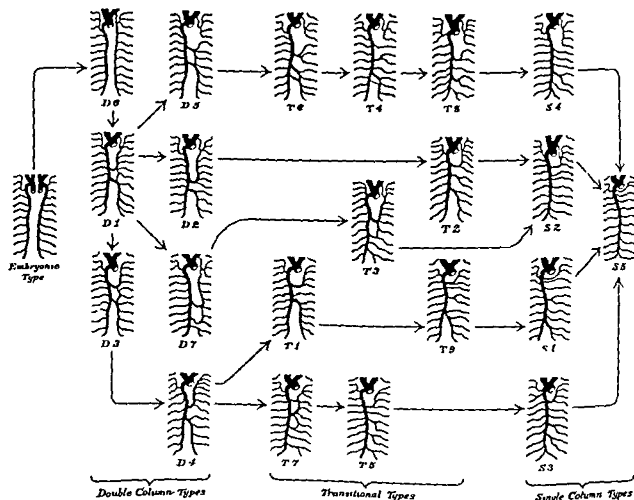


Fig. 1-68A. Patterns in the thoracic portion of the azygos system of veins. Diagrammatic presentation of 21 different types in three major groups encountered in 200 cadavers. Types arranged in structural series, in the order indicated by the arrows. In the double-column group, D, right and left longitudinal veins occur, both unbroken, in the transitional types, T, two, three, or four breaks occur in the left longitudinal vein, in the single-column types, S, five or more breaks occur in the left longitudinal vein (hemiazygos), the unbroken right vein (azygos) receiving most of the left intercostal veins directly. The numerical distribution is as follows in the double-column group of types. D1, 49; D2, 25, D3, 25; D4, 11, D5, 3, D6, 2, D7, 1. In the transition group, these are the totals T1, 22, T2, 20, T3, 13, T4, 5; T5, 5, T6, 4, T7, 2; T8, 2; T9, 1. The distribution in the double-column is among five types. S1, 3; S2, 2, S3, 2, S4, 1; S5, 1.

plexuses by way of intervertebral and lumbar veins. These widespread connections bring the following structures into venous relationship with the kidney: the respiratory diaphragm, the suprarenal gland, testis, ductus deferens, and ureter, the capsular and the general retroperitoneal tissue, the peritoneum, the lumbar, dorsal axial, and appendicular muscles (psoas major, sacrospinalis, quadratus lumborum, latissimus dorsi, and trapezius), the superficial fascia and skin, the ribs, intercostal muscle, thoracic subserous tissue; the pleura and pericardium; the vertebrae, their disks and ligaments; the spinal cord and its meningeal coats, the visceral musculature and skeletal elements of the pelvis, and the lower extremities.

When the parietal portion of the lumbar system of veins is considered apart from its visceral dependencies, similarities to the azygos system are more striking than the differences.

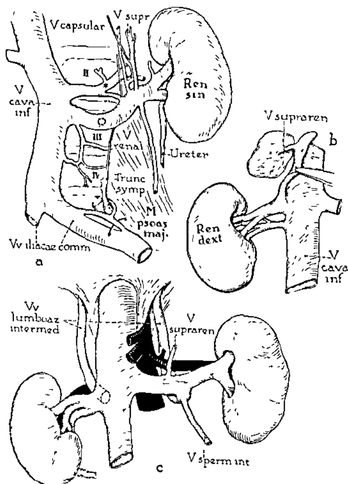


Fig 1-69B. a, Specimen displaying a complex pattern of veins in, or closely related to, the renal pedicle of blood vessels large second lumbar vein (at *) communicating with the renal vein; suprarenal, capsular, and internal spermatic veins likewise ending in the renal vein; third lumbar vein entering (at dotted circle) the dorsal aspect of the renal vein, retroaortic plexus of lumbar veins terminating in the caval, as well as in the renal, vein and thus differing from the fifth lumbar vein, which descends to a side channel of the left common iliac vein (hiatus marked by arrow) b, Dissection showing the typical form of right suprarenal vein, the short vessel entering the dorsal surface of the inferior vena cava, doubling of the right renal vein c, Specimen with exceptionally copacious connections between the renocaval and azygos drainage on the right side and between renogonadal and hemiazygos drainage on the left (From Anson Atlas of Human Anatomy. Saunders, 1950.)

Quite frequently a vein which resembles a typical caval channel at its renal extremity is found to have no iliac segment; in such cases the lumbar veins of the left side cross the vertebral column to the regular (right) inferior vena cava.

When the usual communications of the left renal vein are grouped, as if the observer were viewing a composite of three or four selected specimens, the true expanse of the renal field of vascular influence becomes apparent. The left renal vein is then found situated at the core of an impressive set of venous plexuses and veins: inferior phrenic and suprarenal tributaries enter from above; from below and the side come spermatic (or ovarian), capsular, lumbar, and ascending lumbar veins and anomalous vena cava. Additionally, communication is made with azygos and hemiazygos veins (usually through lumbars) and with the extensive set of internal and external vertebral

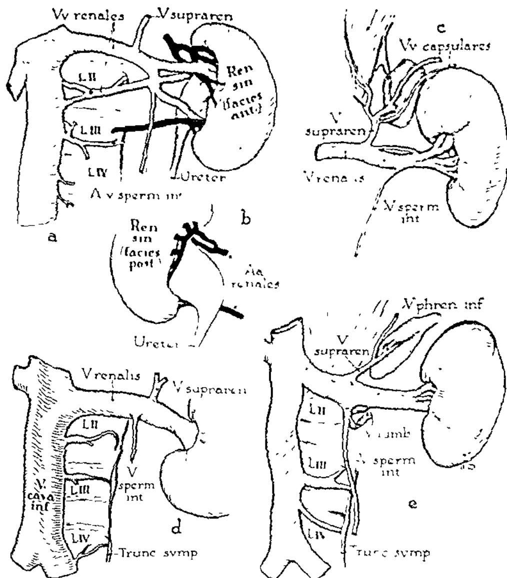


*Fig. 1-69A. Variations in the patterns of the renal, lumbar, caval, and related veins. a, Circum-aortic venous "ring" (actually, of triangular configuration), the preaortic (cranial) limb receives the suprarenal vein; the second lumbar vein terminates in the retroaortic (caudal) limb (at *) Near the renal sinus, both the vein and the artery are double, the course of one of the arteries carrying it to the dorsum of the renal pelvis (as shown in b) c, Common, or "classical" form of left renal vein, which receives, cranially, a common trunk for the inferior phrenic, capsular, and suprarenal tributaries, and caudally, the sex vein (internal spermatic or ovarian). d, The simple pattern, in another specimen; the lumbar veins are tributaries of the caval vein and the left common iliac vein. e, Modification of the preceding pattern, in which the second lumbar vein, joined by the internal spermatic vein, empties into the renal vein.*

constituent would be the caval vein; the lateral component would be the ascending lumbar vein, cranial and caudal elements would be lumbar veins.

As might be expected, one or several of the quadrilateral constituents may be wanting on either or both sides of the same specimen, supernumerary connections (duplications) may occur, obliquely coursing anastomoses are not uncommon.

Any of these features may occur alone, or several of them may be encountered in combination—as two selected specimens will serve to demonstrate. In one of these, *transversely* coursing veins were wanting at the fourth and fifth lumbar levels, and corresponding vessels (duplicated for the second lumbar level) entered an oblique vessel which brought the left renal vein into direct communication with the hemiazygos vein (Fig 1-71).

In the other *specimen*, a full complement of lumbar veins was present, however, the caudal members of the set failed to attain caval connections, and the cranially situated members ended in the renal or a renolumbar tributary of the azygos vein [Fig 1-71(*1*)]

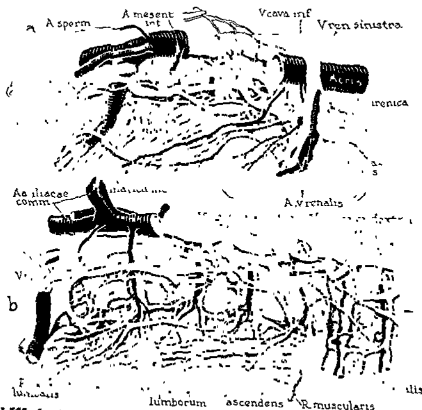


Fig. 1-708. Renal *venous* communications, both parietal (lumbar) and visceral. In this specimen,
a pelvic kidney occurred on the right side, and a circumaortic venous ring and persistent caval
channel on *the left*. *In a*, a segment of the aorta has been excised *to expose* the postaortic limb
of the ring, the arrow *points* to an accessory loop of the left inferior vena cava, which *passed*
ventral to the *common iliac* artery. In *b*, the left *kidney* and portions of both venous limbs have
been *removed*, the *psoas major* muscle has been *dissected away*; the asterisk marks the crest of
the Ilium Key. *A*, Inferior vena cava, B, persistent left vena cava
The ascending lumbar vein
lumbar veins The lumbar
the intermediation
occur side by side
lumbar vein. The
The renal vein div
circumaortic venous *ring*; the deep division receives the left ... nerves of the lumbar plexus.
inferior vena cava and communicates with the hemiazygos vein (*From Anson et al. Surg*, Gynec.
& Obst. 1947; and J. Urol. 1948)

generally, segmental transverse channels enter longitudinal vessels which are paravertebral in position; quite commonly transverse veins from adjacent lumbar "segments" fuse to form a common trunk, the longitudinal vessel may be interrupted at one or at several vertebral levels. The major difference lies in the presence, in the lumbar region, of a third longitudinal vessel, the *inferior vena cava.* The occurrence of this large prevertebral channel (or in some instances, of two caval veins, side by side) results in the production of a ladderlike pattern of vessels—in which, ideally, a lumbar vein at each of five vertebral levels would, on each lateral half of the body, pass transversely between the ascending lumbar vein (deeply situated in the psoas major muscle) and the inferior vena cava (resting upon the median margin of the psoas muscle of the right side). This means that the component vessels would form a series of quadrilateral figures, each covering the area between the middle of one vertebra and the corresponding portion of the next vertebra in either cranial or caudal succession. The medial

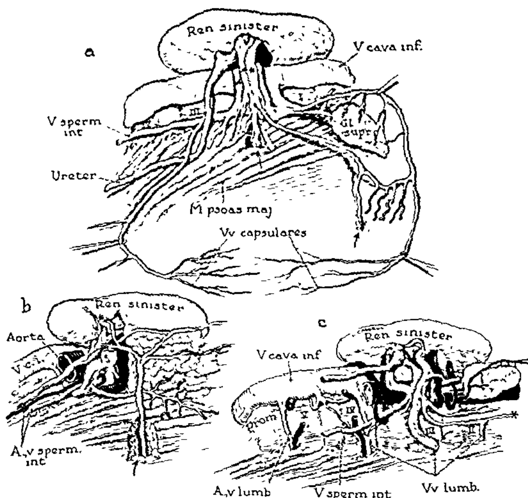


Fig. 1-70A. Lumbar, hemiazygos, and associated tributaries of the left renal vein. The specimens are viewed from the left side, with the kidney in *each case rolled medialward. a,* Division of the renal vein forms preaortic segment (at *) and retroaortic segment (at **) of a circumaortic venous ring (aorta excised in the dissection) The lower capsular vein ends in the internal spermatic vein; the upper vein *divides,* one limb forming a common trunk with the internal spermatic vein, the other limb, after receiving an intercostal tributary (at arrow, lower right) joins the second lumbar vein (at arrow, upper middle) before terminating in the retroaortic limb of the circumaortic venous ring *b,* Lumbar venous (at arrow) communicating with the left renal vein and capsular veins in the retroperitoneal connective tissue The deeper course of the second lumbar vein is demonstrated by dissecting away a portion of the psoas major muscle *c,* Three types of communication of left lumbar veins in a single specimen: second lumbar vein, with the hemiazygos; third lumbar vein, with the renal (after emerging, at arrow, from the psoas major muscle); fourth and fifth lumbar veins, with the inferior vena cava. (From Anson. *Atlas of Human Anatomy* Saunders, 1950)

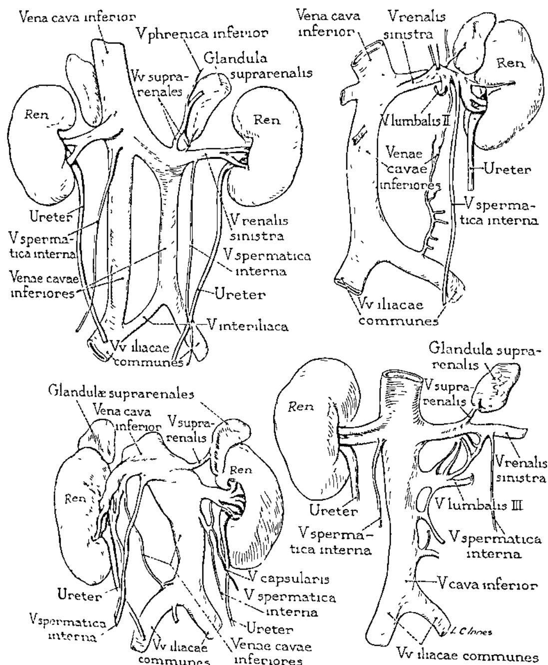


Fig 1·71(1). Types of caval pattern. *Upper left,* right and left venae cavae of approximately equal caliber *Upper right,* small caval vein of the left half of the body. *Lower left,* unusually large left inferior vena cava. *Lower right,* a right caval vein of usual size, accompanied on the left side by a short renolumbar communication

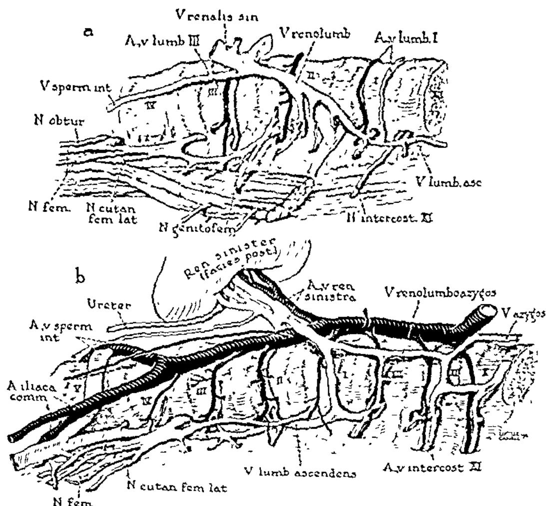


Fig. 1-71. Types of left ascending lumbar vein, in relation to visceral connections in the abdomen and parietal communications in the thorax. In a, the psoas major muscle has been transected, freed from vertebral attachments, and reflected, whereas in b, it has been removed; in a, the left kidney has been removed, while in b it has been lifted on its vascular pedicle. a, In the absence, caudally, of an ascending lumbar vein, the third lumbar vein joins the renal vein near the point at which the latter receives the internal spermatic vein. Cranially, a renolumbar channel partly replaces an ascending lumbar vein. b, A complete and, therefore, "typical" ascending lumbar vein communicates with the azygos and hemiazygos veins of the thorax through a vessel which is a continuation of the renal, rather than of the lumbar, vein. The system as a whole is atypical in that none of the segmentally arranged lumbar veins terminates in the inferior vena cava. (From Anson, Atlas of Human Anatomy. Saunders, 1950.)

The hepatic vessels. The renal vessels

HANS ELIAS

HEPATIC BLOOD VESSELS

The internal anatomy of the liver was known in all detail to Glisson (1654). Yet, today, textbooks of anatomy contain no useful information on the interior of this organ In 1948 and 1951 (Hjortsjo), interest in the subject reawakened, and in 1952 (Elias and Petty), the three vascular systems and the ductal system within the liver were described and coordinated with each other. The liver is the immediate successor of the yolk sac (Elias, 1955b), originating in close relationship to the latter and taking over its principal function, viz., food storage. The liver is a "muralium" (system of connected walls or plates made of liver cells, the *laminae hepatis*). The spaces between the laminae (the lacunae) form the continuous *labyrinthus hepatis* In it is suspended a three-dimensional network of sinusoids (Elias, 1949a, b). The liver can be defined as a muralium inserted in the venous return from the intestine.

The *sinusoids* are lined with flat, potential phagocytes, known as *cells of von Kupffer* It was formerly believed (Wolf-Heidegger, 1941) that two kinds of cells are present in the sinusoid lining Knisely et al (1948), however, showed that all these cells are potentially alike Just as many of these cells are activated as are needed at each moment for the removal of substances from the blood. The belief that the Kupffer cells sit *across* the sinusoid lumen like spiders was shown to be erroneous by Knisely et al (1948) and by Elias (1952).

The histologic architecture of the liver is dependent upon the pressure gradient between portal and hepatic *veins* (Hamperl, 1950, Elias and Sokol, 1953). Under normal conditions, i e., when portal blood pressure is higher than hepatic venous blood pressure, the sinusoids converge radially toward the smallest tributaries of hepatic veins, which, therefore, are called central veins (Kiernan, 1833). The normal liver lobule has such an efferent vein in its axis. But when the hepatic venous pressure increases (passive congestion or experimental ligation of hepatic veins), or when the portal venous pressure decreases (Zahn's infarct, biliary obstruction whereby the engorged bile ducts compress the portal veins, experimental ligation of portal veins), sinusoids and hepatic laminae can be seen radiating from portal canals.

There is much evidence (*Popper, 1931;* Knisely et al, 1948; Mark, 1951; Elias, 1953, Peters, 1956) that small branches of the hepatic artery and of the portal vein, as well as the sinusoids, are provided with *blocking mechanisms* and *sphincters* at various levels. As a result, every small region of the hepatic parenchyma is supplied by either fast-running or stagnant blood of different composition (arterial *and portal)* at various times. Terminal twigs

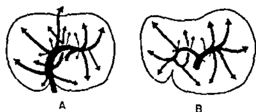


Fig 1-72. Blood supply of the human liver. A, In the fetus, B, in the adult These diagrams explain the decrease in relative size of the left part of the liver after birth (Fig. 1-72 cont on p. 1-176)

The hepatic vessels. The renal vessels

HANS ELIAS

HEPATIC BLOOD VESSELS

The internal anatomy of the liver was known in all detail to Glisson (1654). Yet, today, textbooks of anatomy contain no useful information on the interior of this organ In 1948 and 1951 (Hjortsjö), interest in the subject reawakened, and in 1952 (*Elias and Petty*), *the three vascular systems and the ductal system within the liver were described and coordinated with each other* The liver is the immediate successor of the yolk sac (Elias, 1955b), originating in close relationship to the latter and taking over its principal function, viz, food storage The liver is a "muralium" (system of connected walls or plates made of liver cells, the *laminae hepatis*). The spaces between the laminae (the lacunae) form the continuous *labyrinthus hepatis* In it is suspended a three-dimensional network of sinusoids (Elias, 1949a, b). The liver can be defined as a muralium inserted in the venous return from the intestine.

The *sinusoids* are lined with flat, potential phagocytes, known as *cells of von Kupffer*. It was formerly believed (Wolf-Heidegger, 1941) that two kinds of cells are present in the sinusoid lining Knisely et al (1948), however, showed that all these cells are potentially alike. *Just as many* of these cells are activated as are needed at each moment for the removal of substances from the blood The belief that the Kupffer *cells sit* across the sinusoid lumen like spiders was shown to be erroneous by Knisely et al (1948) and by Elias (1952).

The histologic architecture of the liver *is* dependent upon the pressure gradient between portal and hepatic veins (Hamperl, 1950, Elias and Sokol, 1953). Under normal conditions, i e., when portal blood pressure is higher than hepatic venous blood pressure, the sinusoids converge radially toward the smallest tributaries of hepatic veins, which, therefore, are called central veins (Kiernan, 1833). The normal liver lobule has such an efferent vein in its axis. But when the hepatic venous pressure increases (passive congestion or experimental ligation of hepatic veins), or when the portal venous pressure decreases (Zahn's infarct, biliary obstruction whereby the engorged bile ducts compress the portal veins; experimental ligation of portal veins), sinusoids and hepatic laminae can be seen radiating from portal canals.

There is much evidence (Popper, 1931; Knisely et al, 1948, Mark, 1951, Elias, 1953, Peters, 1956) that small branches of the hepatic artery and of the portal vein, *as well as the* sinusoids, are provided with *blocking mechanisms* and *sphincters* at various levels. As a result, every small region of the hepatic parenchyma is supplied by either fast-running or stagnant blood of different composition (arterial and portal) at various times Terminal twigs

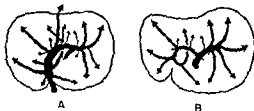


Fig. 1-72. Blood supply of the human liver. *A, In the fetus; B,* in the adult These diagrams explain the decrease in relative size of the left part of the liver after birth (*Fig. 1-72 cont. on p. 1-176*)

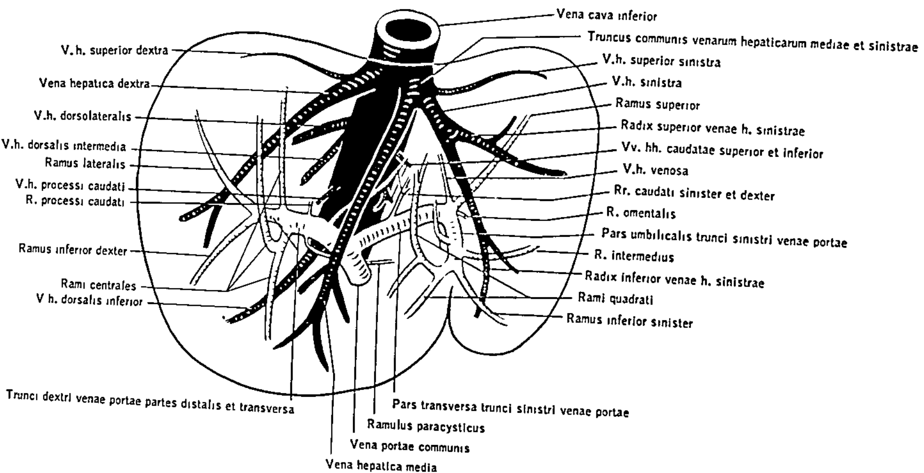


Fig. 1-72 (Cont.). C, Human liver, ventral aspect. Hepatic veins, black; portal vein branches, white.

of the hepatic artery enter into the sinusoids at every lobular level (in the paraportal, intermediate, and central zones).

With advancing age, small cushions or continuous layers of longitudinally arranged, smooth muscle fibers appear in the *tunica intima* of the branches of the hepatic artery (Ehrenbrand and Burckhart, 1956), which, when contracted, block the lumen of the arteries partially or completely.

In the late stages of fetal life, the *umbilical vein* enters the liver at the left from below, sweeps in a great arch toward the right (Fig 1-72A), and gives off several branches to the parenchyma of the liver. Most of the umbilical blood passes through hepatic parenchyma be- [illegible] the [illegible] per cent of cases [illegible], the few cases (20 per cent) in which the ductus venosus is wide, the right half of the liver is degenerated at term because, then, much blood by-passes this part of the organ

As at a "merging traffic" sign, the fetal portal vein joins the end of the umbilical vein at a smooth angle and is directed toward the right.

Thus, when the umbilical vein is ligated at birth, the main blood supply to the liver comes through the portal vein, which is directed toward the right. The remaining intrahepatic portion of the umbilical vein therefore arises from the common portal vein at a sharp angle and bends further in a caudal direction (Fig. 1-72B). Certainly then, while the right half of the liver is hydrodynamically favored, the left half is at a circulatory disadvantage This is why the right half of the liver increases more rapidly in size during early childhood, and the left half lags behind in growth.

The Portal Vein

At the point where the fetal portal vein joins the umbilical vein, there is, postnatally, the bifurcation of the *portal vein* The blood streams from here through the right and left stems of the portal vein (Fig. 1-72C). The *truncus dexter* gives rise to from one to three *rami centrales*, one *ramus lateralis*, and one *ramus inferior dexter* In addition, there are a few minor constant branches, the most important of which is the *ramulus caudatus dexter*.

The *truncus sinister venae portae* has a *pars transversa* and a downward running *pars umbilicalis*. From it arise the *ramus superior sinister*, the *ramus intermedius*, the *ramus inferior sinister*, and several *rami quadrati*. Again there are a few minor branches, among which may be named the *ramulus caudatus sinister*.

The supply territories of the left and right trunks of the portal vein are sharply divided from one another. This is the reason for the sharp demarcation of the area of necrosis in stillborn infants with wide ductus venosus (Gruenwald, 1949).

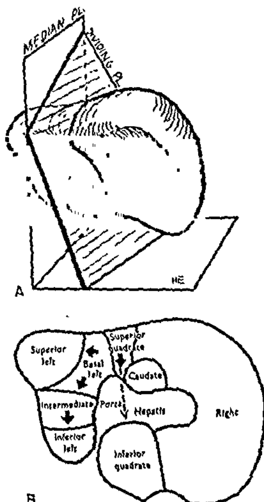


Fig. 1-73 A. Stereogram illustrating the approximate, average position of the plane dividing the *pars umbilicalis hepatis* (left portal territory) from the *pars omphalomesenterica hepatis* (right portal territory) in the human adult. (Based on the description by Hjortsjo.) B. Surgical segments *If one of the segments in which arrows are drawn is extirpated, the one to which the arrow points will be deprived of blood drainage. Therefore, this segment must also be sacrificed to avoid its degeneration.*

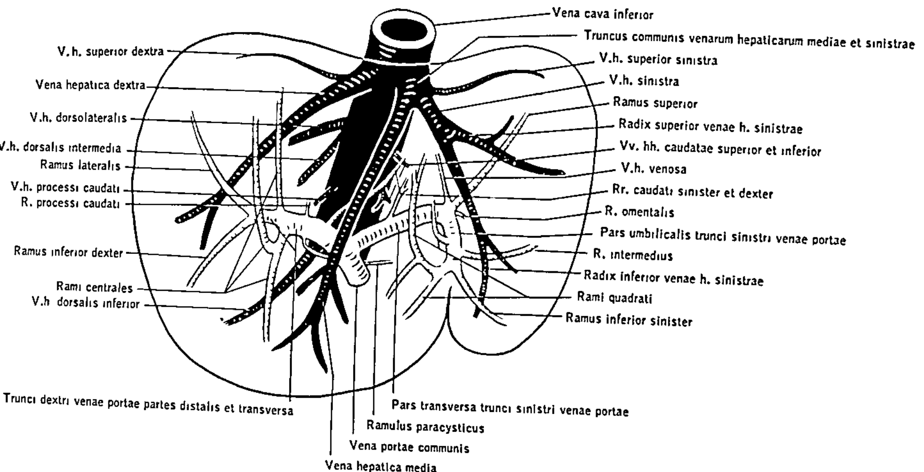


Fig. 1-72 (Cont.). C, Human liver, ventral aspect. Hepatic veins, black; portal vein branches, white.

tory of the rami centrales), and the *vena hepatica dextra* In addition, there are several smaller hepatic veins The *vena hepatica dorsolateralis dextra*, the *vena hepatica dorsalis*, and the *vena hepatica dorsalis inferior*, together with a few smaller ones, enter directly into the inferior vena cava from the territory of the liver which closely surrounds this large vessel Since in this region the vena cava is literally embedded in liver parenchyma, the above hepatic veins are practically inaccessible to surgery.

Each hepatic vein has its own, sharply defined drainage territory (Fig 1-74B). Unfortunately, the hepatic venous segments are not identical with the ductoportoarterial segments, but they interdigitate with them and often overlap them transversely. This arrangement unifies the liver, and makes surgery difficult.

A few anastomoses exist between the small hepatic veins, particularly in the right lobe

The distribution of the portal and of the hepatic veins is rather constant. Therefore, it is possible to develop, from the knowledge of these vessels, a surgical anatomy (Elias, 1954) Since the ducts run (except in the hilus) alongside the portal veins and arteries, preoperative cholangiography will give information of the dividing planes between the portoarterial segments A surgeon thus can avoid large, afferent vessels

However, one cannot remove certain portoarterial segments without interrupting certain hepatic veins which, draining another area, run through the segment to be resected For example, if the segment of the ramus intermedius were resected, the area of the ramus inferior sinister venae portae would be *deprived* of drainage, since it is normally drained by the radix inferior venae hepaticae sinistrae, which runs through the intermediate segment Thus, in this case, the left inferior segment also must be sacrificed *The surgical segments* of the liver are mapped in Fig 1-73B If any segment in which an arrow is drawn should be extirpated alone, that segment to *which* the arrow points would be deprived of drainage and therefore would degenerate *To avoid* this, the surgeon must sacrifice also the segment to which the arrow points Those segments in which no arrow is drawn can be removed without endangering any other part of the liver It is seen that the entire right territory should be considered as one single segment This is because, in this

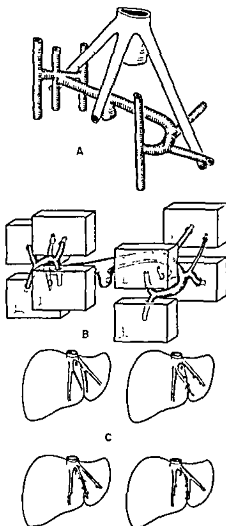


Fig. 1-75. A Schematic presentation of the portal venous system (shaded) and of the major hepatic veins (white). (*After Reifferscheid*) B. Reifferscheid's *concept of portal "segments."* C. Variations of the *radix inferior venae hepaticae sinistrae*. (*After Reifferscheid.*)

territory, the hepatic veins interdigitate to a very high degree with the portal segments. This portion also contains the rami centrales, which are *often* multiple and, therefore, difficult to map.

RENAL CIRCULATION[1]

To the general reader of textbooks of histology, the microanatomy of the kidney appears to be well understood This was the author's impression until he undertook to write a chapter on the kidney for

[1] Only the glomerular circulation is presented here *Editor*.



Fig. 1-74. A. Territories of portal branches of the second, third, and fourth orders are bent apart, and pieces of paper are inserted between them to demonstrate the lack of anastomoses between portal segments. Corrosion preparation of vinyl cast of portal vein branches B. Corrosion preparation of the major hepatic veins of a 3-year-old boy. The veins are slightly bent apart in order to demonstrate the separation of the hepatic venous territories.

The main boundary plane is slightly inclined against the sagittal plane (Fig. 1-73A). This boundary plane runs through the middle of the caudate lobe and through the fossa of the gallbladder. Thus, it is obvious that the quadrate lobe belongs to the left territory.

As shown by splenoportograms, blood from the spleen streams, paradoxically enough, chiefly to the right side of the liver as a result of streamlining in the common portal vein The two streams (from the superior mesenteric and from the splenic vein) cross spirally, in much the same way as the blood streams in the truncus arteriosus While, in the latter, a septum separates the pulmonary from the aortic streams, in the portal vein, the two streams remain separated without any intervening septum.

Each branch of the portal vein has its own, sharply defined territory (Fig. 1-74A), and no anastomoses occur between neighboring portal vein territories This applies to the large rami as well as to the smallest branches Each segment of the portal vein is supplied by a specific branch of the hepatic artery and is a drainage territory of a specific root of the hepatic duct.

While a strict coordination of portal, arterial, and ductal territories takes place within the mass of the liver, an irregular and unpredictable arrangement of the *hepatic arteries* and *ducts* occurs in the region of the *porta hepatis*, that large mass of connective tissue which appears to be pushed into the body of the liver on its dorsocaudal surface. This territory of irregularity stretches from the extremity of the truncus dexter to the extremity of the pars umbilicalis trunci sinistri venae portae.

Many variations of the arterial and ductal pattern have been reported, but, as soon as the vessels and ducts have entered into the parenchyma of the liver, strict coordination of the "portal triad" prevails (Elias, 1953).

As there are no intrahepatic anastomoses of hepatic artery branches, ligation of any branch of the hepatic artery inevitably leads to degeneration of the territory supplied by it. More than one artery may supply the liver, but each of them is independent of the others and has its own territory of distribution

On the microscopic level, on the other hand, arterial and ductal anastomoses are numerous, since both the arterial branches and the ductal roots form a loose basketwork around the portal veins.

The Hepatic Veins

The liver is drained of blood by three large *hepatic veins* (Fig. 1-72C). the *vena hepatica sinistra*, the *vena hepatica media* (which runs in the main boundary plane and receives radicals from the quadrate lobe and from the terri-



Fig. 1-77. A A podocyte, i.e., a cell of the visceral epithelium of the glomerular capsule, is an extremely complicated cell with many penniform processes (trabeculae) which interdigitate with one another. These trabeculae are not unlike legs, with each one having many little feet (pedicles) The podocyte "sits" on them and is elevated by them above the level of the lamina densa (= basement membrane). Many of the trabeculae and pedicles are covered by parts of the body of the podocyte The endenchyma is included between the folds of the lamina densa; three nuclei of the endenchyma are shown. Blood channels tunnel the endenchyma, but since they are located in a peripheral position, only an extremely thin fenestrated sheet of endenchymal cytoplasm (lamina fenestrata) remains between a blood channel and the lamina densa The parietal layer of the glomerular capsule appears at the left. (*Drawing adapted from Zimmermann; Oberling, Gautier and Bernard, Kulenkampff and Hall. Membranous extension of the podocyte to the left drawn from unpublished electron micrograms by Hall*) B The complete filtration membrane consists of the attenuated portion of perforated endenchymal (endothelial) cytoplasm, called the lamina fenestrata, the lamina densa which in some but not all electron micrograms appears to have many minute pores, and the interdigitating pedicles Depicted in this drawing are the pedicles from four adjacent trabeculae. (*Stereogram based on the electron micrograms of Hall and Pease*)

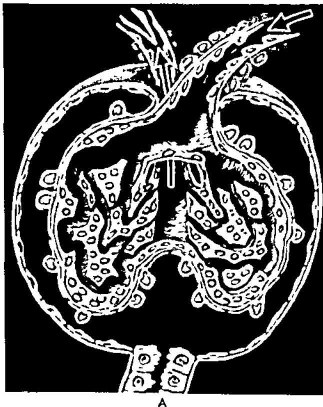
glomeruli in living animals Analysis of the renal glomerulus should begin with the simplest problem and then proceed in order of increasing complexity. For a schematic presentation of the entire renal corpuscle, see Fig 1-76A

RAMIFICATION OF GLOMERULAR CAPILLARIES

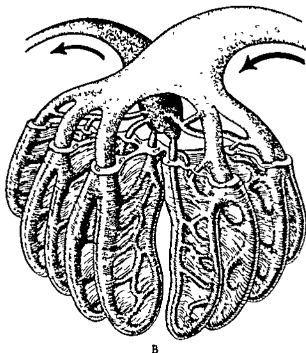
Borst, who presented an exceptionally well-organized description of the glomerulus, first drew attention to the fact that the *vas afferens* forms a relatively large chamber at the point at which it enters the glomerulus, a characteristic which Bowman (1842) had illustrated, although it is questionable whether he was aware of the significance of this characteristic This chamber gives rise to from two to five thick trunks All the branches of each of these trunks constitute a lobe of the glomerulus From personal observations, it would appear that some of the capillaries of separate lobes anastomose with those of other lobes, however, other investigators are of the opinion that such anastomoses occur only at the ends of lobules. This observation was confirmed by Hall (1955).

In the personal observation of 100 glomeruli of canine kidneys, injected with latex, the greatest number of anastomoses observed in a single lobe was five. In other glomeruli, fewer anastomoses, or none, were found In two reconstructions of five glomeruli from one human kidney, there were no anastomoses, while in three there were many This apparent discrepancy may be due to the ability of these connecting channels to open and close (Elias, 1956). Transillumination of living frog glomeruli showed that few or many blood channels in a glomerulus may be open at any one time Anastomoses are more frequent during diuresis when many of them are open

It is rarely possible to force the injection mass through the glomerular capillaries into the *vas efferens*; probably this is because of some yet unknown mechanism of resistance which may also be an important contributing factor to the filtration pressure exerted in the glomerulus. A part of this mechanism may be found, and was described by Borst, in the



A



B

Fig. 1-76. A This bipolar capillary insert into an arteriole is so bent that afferent and efferent vessels lie close together at the vascular pole B Schematic stereogram of the structure of the glomerulus. The blood channels course in a branched sheet, the lamina vasculosa glomeruli

a textbook of functional microanatomy. In reading the newer literature, it became apparent that the more minute structures of the various portions of the nephron have only recently begun to be understood. This advance in understanding had to await the advent of electron microscopy, and only since about 1950 has it become possible to use this instrument for histologic study.

The first investigators to use the more advanced methods of electron microscopy for studying the kidney structure were Hall, and Sjöstrand and Rhodin. To Hall is owed a major part of the present knowledge of the structure of the renal glomerulus, and the present text is based chiefly on his pioneer work. The Swedish investigators concentrated their efforts on studying the proximal convoluted tubule, Henle's loop, and the distal convoluted tubule.

It is well known that the renal glomerulus consists of a tuft of capillary vessels, without musculature, which tuft is inserted in the course of an arteriole However, the structure of the renal glomerulus has been a matter of controversy since the end of the last century As a result of Hall's studies, most of the controversial difficulties can be resolved The points of disagreement are concerned with the following questions.

1. Is the glomerulus covered by epithelium, that is, by a visceral leaf of the glomerular (Bowman's) capsule?

2 Are there perforations in the walls of the glomerular capillaries?

3 Is the endothelium of the glomerular capillaries continuous?

4 Are the loops of the glomerular capillaries supported by connective tissue in a manner similar to that of the mesentery which supports the intestinal loops?

5 Do the glomerular capillaries form anastomosing networks?

6 Is the basement membrane of the glomerulus double or single, i e , does it consist of a basement membrane derived from the glomerular epithelium and of another one derived from the glomerular capillaries, or is there only one common basement membrane?

Practically all these problems can be resolved if the contradictory reports obtained through use of the optical microscope are evaluated in the light of electron microscopic observations and those of transillumination of

appeared to touch a capillary lumen He concluded that those which in single section appeared not to touch a lumen were not endothelial cells but fibroblast-like mesenchymal elements. He recognized as true endothelial cells only those which he saw in contact with a capillary lumen. He considered their cytoplasm to be lighter, and their nuclei to be flatter, than in cells which did not touch a capillary lumen. He also stated that those cells which he called endothelial were separated from the others by an extremely thin membrane, the "proper basement membrane of the capillaries." He thought that those cells within the folds of the basement membrane, which did not seem to be in contact with a capillary lumen, constituted a supporting tissue for the glomerular capillaries, he called this tissue a "mesangium" and compared it with the mesentery which suspends the gut Goormaghtigh and Bohle and Kreeke accepted his idea and developed it further. Bohle and Herfarth, however, later admitted that connective tissue elements exist only in the proximity of the hilus in the space between the vascular and the glomerular basement membrane This scanty amount of connective tissue reaches only to the level of junction of both basement membranes.

However, from Hall's studies with the electron microscope, it became evident that no cytologic difference could be detected between the cells touching the capillary lumen and those which apparently are not in contact with it Consequently, he concluded that they were all endothelial cells For reasons explained below, the author calls them "endenchymal" cells. Hall is convinced that every endothelial (endenchymal) cell touches a capillary lumen In order to verify this, the author prepared [illegible]

[illegible] between [illegible] layers of the basement membrane touches a vascular lumen Thus, further proof was obtained that a so-called mesangium does not exist, except near the hilus (Bohle and Herfarth). Neither Hall nor Elias studied the hilar regions of the glomerulus

According to Vimtrup, whose point of view has been accepted by most investigators, the glomerular blood channels are cylindric capillaries, each surrounded by its own cylindric basement membrane.

The author analyzed the architecture of the renal glomerulus by the statisticogeometric method and verified his results by three-dimensional models from serial sections This method permits extrapolation from two-dimensional sections to three-dimensional space. A section through a cylinder, for example, is an ellipse, and its axial ratio equals the cosecant of the angle between the long axis of the cylinder and the cutting plane A section through a disk resembles a trapezoid, and its length and width are functions of the cutting angle and of the distance of the section from the center of the disk. The percentage distribution of the axial ratios of sections can be predicted from these basic facts and from a consideration of the random arrangement of these bodies in space.

Similarity of blood channels to cylinders became evident. However, the portions of the glomerulus lined by basement membrane are flat laminae, the *laminae vasculares glomeruli*. They are branched; this property marks them as being geometrically "flatter" than simple disks. Within these laminae, course the cylindric blood channels (Fig 1-78B).

Thus the folds of the basement membrane enclose a continuous, flat, and branched mass of cells tunneled by hollow, cylindric channels through which blood flows. This tissue, being continuous with the endothelium of the vasa afferens and efferens, is a part of the endothelial system However, even though blood touches every cell of this tissue, it is not endothelium in the ordinary sense, and therefore it has been proposed to introduce the term *endenchyma* for this type of tissue.

An endenchyma may be defined as a continuous mass of cells within a basement membrane; this mass of cells is tunneled by channels through which blood flows but without basement membranes [illegible]

nc [illegible]

th [illegible]

str [illegible] three sides

Hall, by determining the area of free lamina densa available for filtration, made it most plausible that the pedicles of the podocytes may play an essential role in regulating the glomerular filtration rate. Their presence over the entire surface of the basement membrane, including portions covering solid endenchyma, would not be rational from a physiologic point of view, since filtration could not

constrictions of the capillary lumina at points of ramification, and in the course of undivided capillaries. Another factor is the continuous tapering off of the glomerular capillaries from their origin to their entrance into the collecting trunk that empties into the vas efferens. In addition, there may be a mechanism, perhaps *sphincterlike* or *valvelike*, at the entrance of the collecting trunk into the vas efferens. This mechanism is possibly similar to the "outlet sphincters" which can be found at the points of entrance of the liver sinusoids into the hepatic veins, as described by Knisely, Bloch, and Warner (1948).

The vas efferens begins, as Borst observed, with a large, frequently elongated chamber of even diameter. The collecting trunks enter this chamber. One collecting trunk usually carries the blood from one lobe, but occasionally the blood from two adjacent lobes may be mixed in one collecting trunk.

An occasional feature of both the vas afferens and the vas efferens is the droplike protrusion of endothelial nuclei into the lumina of these vasa, these nuclei point in the direction of blood flow, as described by Zimmermann and observed by other authors (Fig 1-76A).

FOLDING OF THE BASEMENT MEMBRANE

In his study of the glomerulus, Zimmermann demonstrated that the basement membrane of the glomerulus appeared to be continuous with that of the basement membrane of the parietal leaf of Bowman's capsule and with the vasa afferens and efferens. Bohle and Krecke, as well as the author, have recently confirmed this observation. Bohle and Herfarth found that the basement membrane of the vas afferens unites with the glomerular basement membrane a short distance from the vascular pole. Borst compared the basement membrane of the glomerulus to "a gown thrown into many folds which invest the capillary tuft without actually forming true tubes." Borst stated that the capillary lumina were in direct contact with the basement membrane. Zimmermann and Bohle and Krecke, on the other hand, stressed that the basement membrane of Bowman's capsule belonged to the epithelium and that, therefore, there should be a separate basement membrane of the capillaries within the former. They described this capillary basement membrane as being extremely thin but failed to document this opinion. Hall, using the electron microscope, has shown that *there is only one basement membrane*, this is the "lamina densa" described below.

THE ENDENCHYMA

The tissue found within the folds of the glomerular basement membrane has been variously described. Von Mollendorff (1927) published excellent illustrations of the folding of the membrane. Zimmermann noticed that the folds of the basement membrane were partially filled by a continuous mass of cells. In tissue sections, he noticed that not all these cells

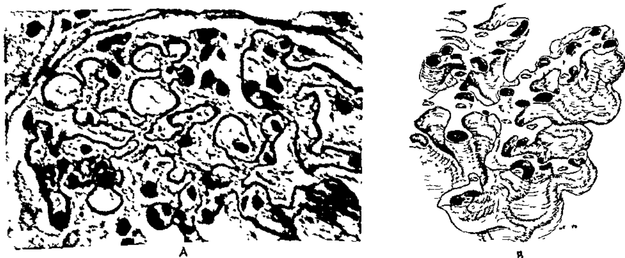


Fig. 1-78. A. Section of human glomerulus, 2 μ. B. Reconstruction of part of lamina vasculosa glomeruli of man.

ment membrane (*lamina densa* of Hall) is substantially through the little feet, or pedicles. Beneath the podocyte is a subpodocytic space. Also, their larger processes "sit" on the lamina densa by means of a narrow ridge Slightly broader contacts exist at a few locations, and from the axial basal contact ridge of each trabecula, the pedicles project laterally, not unlike needles from the twig of a fir tree.

The pedicles are about 1 μ long, and each ends in a little knob Pedicles from neighboring trabeculae interdigitate with each other. *Entire* trabeculae may be seen in subpodocytic spaces. Trabeculae may not only radiate from the cell bodies peripherally but also arise from the undersides of the podocytes The entire basement membrane is covered by the interdigitating, pennate processes of the podocytes, and thus the podocytes themselves are elevated

LAMINA FENESTRATA (ATTENUATED PORTION OF ENDENCHYMA)

Endenchymal cells are present in several of Hall's electron micrograms. A transition of the endenchymal cell body into an extremely thin, cribriform cytoplasmic layer, which extends along the basement membrane, is often visible.

This extremely thin layer of endenchymal cytoplasm in ultrathin tangential sections of the outer capillary walls *presents the aspect of a* sieve, the pores of which measure from 400 to 1,500 A (0.04 to 0.15 μ) in *diameter Hall* has called this attenuated sheet of endothelial *cytoplasm* the lamina fenestrata

It appears to the writer that a *formation* which occurs with such *regularity with different* fixation methods must have a *background* of reality and is *probably not an artifact*. The term lamina fenestrata is a good one and should be *retained*.

Lamina Densa (Glomerular Basement Membrane)

Compared with the lamina fenestrata, the *basement* membrane is rather thick, from 800 to 1,200 A (0.08 to 0.12 μ) Through the electron microscope, *it* appears at times to consist of three layers Hall *called it the lamina densa*. In tangential sections, one *can notice*, *when* looking through the large pores of the lamina *fenestrata*, what appear to be extremely small *pores in the lamina* densa These small pores measure about 100 A (0.01 μ) or less *in diameter*. Newer observations, employing better methods, do not show the small pores.

COMPLETE FILTRATION MEMBRANE

The glomerular wall, which separates the *blood from* the space *within the* Bowman's *capsule, is composed of three layers, shown schematically in Fig* 1-57B.

1. The internal layer is the cribriform, attenuated portion of endenchymal cytoplasm, *the lamina fenestrata*. It has large pores, approximately from 400 to 800 A (0.04 to 0.08 μ) wide.

2. The intermediate layer *is the definitive basement membrane, or lamina densa, a relatively* thick membrane (approximately 800 to 1,200 A) with pores 100 A wide, small enough to retain the molecules of those substances which are known to be retained in the renal corpuscles. The existence of these small pores has not been confirmed.

3. The outer layer is composed of the interdigitating *terminal processes*, the pedicles of the podocytes. The spaces between them which, in Hall's early electron micrograms, vary *in* width between 200 and 400 A (0.02 and 0.04 μ), are not seen in more recent pictures by Pease (1955) while they are visible but narrow in those of Yamada (1955).

Hall *suggests* that the pedicles may be actively varied *in width and* thus may control the rate of filtration by changing the *free surface* of lamina densa available for filtration at any time. Oberling, Gautier, and Bernhard suggest, less plausibly, that the function of the pedicles may be that of a suction pump.

The interpedicellar spaces open into the subpodocytic *space*. Hall *is* of the opinion that these spaces also open into the free capsular space. If in life the subpodocytic *space communicates* with the space of Bowman's capsule, as it appears to do in many electron micrograms, then the structure of the filtration membrane, *as revealed* by Hall's studies, strongly supports the *mechanism of filtration* as postulated by physiologists

In many electron micrograms, an *extremely* fine, membranous extension of the podocytic *cytoplasm* is evident. This membrane is so thin that *it will* break easily in the preparations Therefore, *its frequent* absence in electron

take place at such locations if they were so located permanently. It is possible to assume that, during life, the vascular lumens shift from place to place so that filtration can occur from time to time at each location of the pedicle-studded basement membrane.

As verified by transilluminating living frog glomeruli (unpublished findings), the positions of blood channels in such cellular tissue are indeed not permanently fixed. The endenchyma facilitates fusing of formerly separated channels or splitting of a single channel in two. It also facilitates the establishment and elimination of anastomoses and, therefore, accounts for diverging opinions regarding anastomoses; this explains why individual glomeruli of the same kidney appear different Shifting of blood channels is a rapid process, cyclic, transverse movement taking only a second or less.

Another special property of the glomerular endenchyma is its mechanical function. The blood pressure in the glomerulus, being considerable, should force the opposing layers of basement membrane apart to form a balloon of blood far exceeding the size of a single renal corpuscle. However, the endenchymal sheet remains extremely thin (5 μ between the thinnest places). Therefore, great tensile strength and adhesiveness must be ascribed to the endenchyma as it holds these layers together Since, on cross section through the equator of a glomerulus, the total length of the section of basement membrane has been found to be about 1,000 μ, it follows that a balloon of about 300 μ in diameter would be formed if the tensile strength and adhesiveness of the endenchyma were abolished This balloon is 1½ times larger in diameter than the normal renal corpuscle, including the space of Bowman's capsule and both the parietal and visceral capsular epithelium, which together normally exceed twice the mass of the glomerulus. Allen has noted that such inflation of single lobes of a glomerulus does occur in diabetic glomerulosclerosis.

Layer of Podocytes (Glomerular Epithelium)

On its outer side, the glomerular basement membrane is covered by the visceral sheet of Bowman's capsule. The cells which compose it (*Deckzellen*—covering cells of von Möllendorff and Bargmann or epicytes of Kulenkampff) project steeply into the capsular space.

Von Mollendorff and Bargmann observed long, slender processes of these covering cells when preparations were stained with iron hematoxylin. Bargmann also observed that a covering cell may extend across a crevice between two capillaries. Zimmermann, using the light microscope, demonstrated the long, penniform processes of the covering cells and described them as similar to twigs of fir trees.

Further information concerning these covering cells, which constitute the glomerular epithelium, can be obtained only by electron microscopy. The first to study the kidney under electron microscopes were Pease and Baker, who thought that many of the processes and their side branches, resembling the needles of fir trees, were reinforcing ridges of the basement membrane. Hall, independently of Zimmermann and Kulenkampff and by means of the electron microscope and improved techniques, showed that *the penniform processes belong entirely to the cells covering the glomerulus on the outside*, that is, to the visceral epithelium of Bowman's capsule.

These observations have been recently confirmed by several authors In shape, these cells are perhaps the most complicated. Oberling, Gautier, and Bernhard said: " . . we have been astounded by the appearance of unsuspected, bizarre structures of unprecedented complexity which it was possible to interpret only by patiently assembling all the observed shapes, much like the pieces of a three-dimensional jigsaw puzzle."

For a correct description we must turn to Hall's electron micrograms. With magnifications of 10,000 diameters, the impression is that the projections seen on the basement membrane are sections of ridges which are parts of the membrane. At a magnification of 45,000 in diameter, however, it becomes clear that these structures are superimposed on the basement membrane like little feet (thus the name pedicles) The entire glomerular epithelial cell of which these little feet are a part he termed a *podocyte* (Fig 1-77A).

The cell body of a *podocyte* is plump; its nucleus is finely granular. It has deep incisions, between which there are ridges. The contact of a cell body of a podocyte with the base-

ment membrane (*lamina densa* of Hall) is substantially through the little feet, or pedicles. Beneath the podocyte is a subpodocytic space. Also, their larger processes "sit" on the lamina densa by means of a narrow ridge. Slightly broader contacts exist at a few locations, and from the axial basal contact ridge of each trabecula, the pedicles project laterally, not unlike needles from the twig of a fir tree.

The pedicles are about 1 μ long, and each ends in a little knob Pedicles from neighboring trabeculae interdigitate with each other. Entire trabeculae may be seen in subpodocytic spaces. Trabeculae may not only radiate from the cell bodies peripherally but also arise from the undersides of the podocytes The entire basement membrane is covered by the interdigitating, pennate processes of the podocytes, and thus the podocytes themselves are elevated

LAMINA FENESTRATA (ATTENUATED PORTION OF ENDENCHYMA)

Endenchymal cells are present in *several of* Hall's electron micrograms A transition of the endenchymal cell body into an extremely thin, cribriform cytoplasmic layer, which *extends* along the basement membrane, is often visible.

This extremely thin layer of endenchymal cytoplasm in ultrathin tangential sections of the outer capillary walls presents the aspect of a sieve, the pores of which measure *from 400 to* 1,500 A (*0 04 to 0 15 μ*) in diameter Hall has called this attenuated sheet of endothelial cytoplasm the lamina fenestrata.

It appears to the writer *that a formation* which occurs with such regularity *with different* fixation methods must have *a background* of reality and *is probably not an artifact*. The term lamina fenestrata is a good one and should be retained.

Lamina Densa (Glomerular Basement Membrane)

Compared with the lamina fenestrata, the basement membrane is rather thick, from 800 to 1,200 A (0 08 to 0.12 μ). *Through the* electron microscope, it appears at times to consist of three layers Hall called *it the lamina densa In tangential* sections, one can notice, when looking through the large pores of the lamina fenestrata, what appear to be extremely small pores in the lamina *densa These* small pores measure about 100 A (0 01 μ) or less in diameter. Newer observations, employing better methods, do not show the small pores.

COMPLETE FILTRATION MEMBRANE

The glomerular wall, which separates the blood from the space within the Bowman's capsule, is composed of three layers, shown schematically in Fig 1-77B.

1. The internal layer is the cribriform, attenuated portion of endenchymal cytoplasm, the *lamina fenestrata*. It has large pores, approximately from 400 to 800 A (0 04 to 0 08 μ) wide.

2 The intermediate layer is the definitive *basement membrane*, or *lamina densa*, a relatively thick membrane (approximately 800 to 1,200 A) with pores 100 A wide, small enough to retain the molecules of those substances which are known to be retained in the renal corpuscles The existence of these small pores has not been confirmed.

3 The outer layer is composed of the interdigitating terminal processes, the pedicles of the podocytes The spaces between them which, *in Hall's* early electron micrograms, vary in width between 200 and 400 A (0 02 and 0 04 μ), are not seen in more *recent pictures* by Pease (1955) while they are visible but narrow in those of Yamada (1955).

Hall suggests that the pedicles may be actively varied in width and thus may control the rate of filtration by changing the free surface of lamina densa available for filtration at any time Oberling, Gautier, and Bernhard suggest, less plausibly, that the function of the pedicles may be that of a suction pump.

The interpedicellar spaces open into the subpodocytic space. Hall is of the opinion that these spaces also *open into the free* capsular space If in life the subpodocytic space communicates with the space of Bowman's *capsule*, as it appears to do in many electron micrograms, then the structure of the filtration membrane, as revealed by Hall's studies, strongly supports the mechanism of filtration as postulated by physiologists.

In many electron micrograms, an extremely *fine*, membranous extension of the podocytic cytoplasm is evident This membrane is so thin that it will break *easily in the* preparations Therefore, its frequent absence in electron

micrograms does not prove its absence during life. Thus, *if the spaces under the podocytes and between their processes are entirely covered by the cell bodies and by their membranous extensions, future studies must show how the primary urine can pass through the podocytes and their membranous extensions to reach the space of Bowman's capsule.* Personal observations by the author have revealed a thin layer of widely spaced podocytes in the desert-dwelling lizard *Phrynosoma* and a dense layer of tall and tightly packed podocytes in the water-dwelling alligator. These observations suggest that the podocytes, rather than inhibiting filtration, may facilitate it.

Some of Hall's electron micrograms show openings in the cytoplasm of the podocytes. *These openings may be sections of vacuoles* which perhaps contain primary urine on its way from the subpodocytic space into the space of the glomerular capsule. In other words, the passage of primary urine through the layer of podocytes *is* perhaps accomplished by pinocytosis. This *is* but one possibility that might be considered.

Unfortunately, it must be concluded that, although the electron microscope has greatly contributed to knowledge of the microanatomy of the glomerulus, the filtration process in the renal glomerulus is still imperfectly understood.

12

The structure of blood vessels

HANS ELIAS

ARTERIES

The structure of the wall of arteries varies according to the size of the artery, but in general, all layers are well developed (Fig 1-80F, G, H).

Internally, there is the endothelium. The *lamina intima propria* is normally thin, although with advancing age, it becomes thicker The *membrana elastica interna* is external to this layer and is frequently corrugated (Fig. 1-80G) Figure 1-80F shows a medium-sized artery of a man of about 50 years of age. The membrana elastica interna of arteries of this size consists, according to Benninghoff (1927), of broad, anastomosing, elastic bands, sometimes of two systems of elastic bands crossing each other. In large arteries, this layer is a fenestrated membrane; in small and medium-sized arteries, a net of elastic bands, and in the smallest arteries, a network of fibers (Fig. 1-81G)

The *tunica media* is thick and consists often of circular, smooth muscle cells, intermingled with elastic fibers, illustrated only in the upper area (Fig. 1-80F). All layers of an artery can be seen in histologic sections (Fig. 1-80H), and when stained with resorcin-fuchsin, the elastic elements are clearly seen (Fig. 1-80G).

Goerttler (1934) and Fischer (1951) have shown that in many arteries, the bundles of circular muscle fibers are continuous into *an outer* and *an inner spiral layer* of varying pitch Left and right winding spirals cross, so that the contraction remains symmetric Contraction of fibers with a pitch smaller than 45° results in narrowing of the artery Those of steeper pitch cause mainly shortening of the artery and widening of the lumen Since flat pitch or circular course is more common, narrowing is the usual effect of contraction (Fig. 1-84B).

Contraction of the muscle fibers causes also thickening of the endothelium (Fig 1-80C). The muscular contraction of the tunica media of blood vessels is influenced by the vasomotor nerves, hormones, and products of metabolism.

In the wall of the aorta, according to Benninghoff, some of the muscle fibers of the media are attached to the elastica interna by means of elastic cell tendons (Fig. 1-81F). Other muscle fibers pierce the elastica interna and spread out slightly on its internal side The contraction of these muscle cells controls the corrugations of the elastica interna. The fenestrated membranes of the media are connected by muscle fibers. Figure 1-81E shows that contraction of the muscle fibers causes corrugation of the membranes

In the *smallest arteries*, the tunica media is relatively thickest There is a ratio of muscle to elastic tissue which varies with the increase in the size of an artery. That is, the shock-absorbing elastic tissue predominates in the large arteries close to the heart and decreases in the smaller arteries On the other hand, muscular tissue composes the bulk of the smaller vessels.

The arteries in Fig 1-81G are drawn to proportion The large conducting arteries possess elastic membranes in their tunica media (upper left) While most of these membranes are fenestrated (perforated by holes), the internal elastic *membrane* is solid. The fenestrated membranes are connected with each other by

micrograms does not prove its absence during life. Thus, if the spaces under the podocytes and between their processes are entirely covered by the cell bodies and by their membranous extensions, future studies must show how the primary urine can pass through the podocytes and their membranous extensions to reach the space of Bowman's capsule. Personal observations by the author have revealed a thin layer of widely spaced podocytes in the desert-dwelling lizard *Phrynosoma* and a dense layer of tall and tightly packed podocytes in the water-dwelling alligator. These observations suggest that the podocytes, rather than inhibiting filtration, may facilitate it.

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means of elastic bands (Fig 1-81A). With decreasing size, the inner elastic membrane becomes fenestrated and dissolved into bands, and in the extremely small arteries and arterioles, it is only a system of longitudinally or spirally arranged fibers, connected by an extremely thin basement membrane

Outside the media is a condensed network of elastic fibers, the *membrana elastica externa* This layer blends with both the tunica media and the adventitia (Fig 1-80F, G).

The elastic membranes can be stained with resorcin-fuchsin (Fig 1-81B). However, if the wall of a conducting artery is stained with hematoxylin and eosin, the muscular tissue of the media will appear darker than the elastic membranes (Fig 1-81C). The amount of elastic tissue in the elastica externa of tortuous arteries is particularly great (Fig 1-82F). From the highly elastic walls of these vessels, the onrushing blood is reflected around the bends much as a billiard ball is reflected by the rubber cushions at the margins of a billiard table (Fig 1-82G). Thus, the velocity of blood flow remains undiminished along the entire course of the artery as long as the vessel does not branch Yet the reflections occur at infinitesimal intervals (Fig. 1-82H). Consequently, the blood flow in tortuous arteries is just as smooth as in straight arteries

In some organs, especially in those which undergo periodic changes of size, as the uterus, the arteries are tortuous Here the tortuosity serves another important function, for when the organ expands, as the uterus during pregnancy, the arteries are effortlessly straightened out.

The *tunica adventitia* is the outer connective tissue layer, which consists of a mixture of elastic and collagenous fibers Fritsche showed that some of the collagenous bundles of the adventitia of the vessels in the extremities have a spiral course of low pitch and that they are continuous with the fibers of the intramuscular septa, and perhaps even of the perimuscular faciae. Thus, the arteries as well as the veins are, to translate his expression, "built into" the extremities.

The wall of blood vessels of medium and large size has its own blood supply through the network of the *vasa vasorum* (Fig. 1-83A).

Muscular cushions, rings, polyps, polsters, and funnels belonging to the intima (occasionally also involving the media and even the adventitia) project into the lumen of arteries in certain organs, controlling blood flow. The arteries which supply the penis have such blocking mechanisms, a fact which has been known for a long time. The description of such "throttles" in numerous other organs has been revived recently (Watzka, Conti, Parvis, Castigli, Ehrenbrand and Burckhart). In the helicine arteries of the corpora cavernosa, they are of particular interest, since they are usually contracted and reduce blood flow to the cavernous spaces to a mere trickle. Erection of the corpora cavernosa penis results from relaxation of the intimal muscle cushions Thus the lumen of the arteries becomes free and the cavernous spaces fill rapidly

ARTERIOLES

The transition from arteries to arterioles is gradual and is marked by a thinning of the vessel walls and a decrease in the size of their lumens The intima consists of endothelium, and the membrana elastica interna consists of very thin, mostly longitudinal fibers (Fig. 1-80D). The tunica media is made of a single layer of circular or spiral smooth muscle fibers (Fig. 1-80A). Occasionally, one smooth muscle fiber may wind several times spirally around an arteriole (Fig. 1-80B). The adventitia of small arterioles consists of connective tissue elements (Fig. 1-80E). The inner, longitudinally arranged nuclei pertain to endothelial cells. As the smooth muscle cells of the media are circularly arranged, the nuclei of some of

left is made of a single endothelial cell Only the nuclei are stained, but they reveal the number of cells G Endothelial cell boundaries can be revealed by silver impregnation. H Very thin capillaries, as in (F) left, are surrounded by a single endothelial cell I Usually the capillary wall (endothelium) is extremely thin and permeable to electrolytes and other substances with small molecules J When the capillary is narrowed, its wall is thick. Narrowing is (perhaps) accomplished by endothelial contraction K Others believe that a specialized, contractile pericyte is needed for capillary narrowing. (From Elias, 1950)

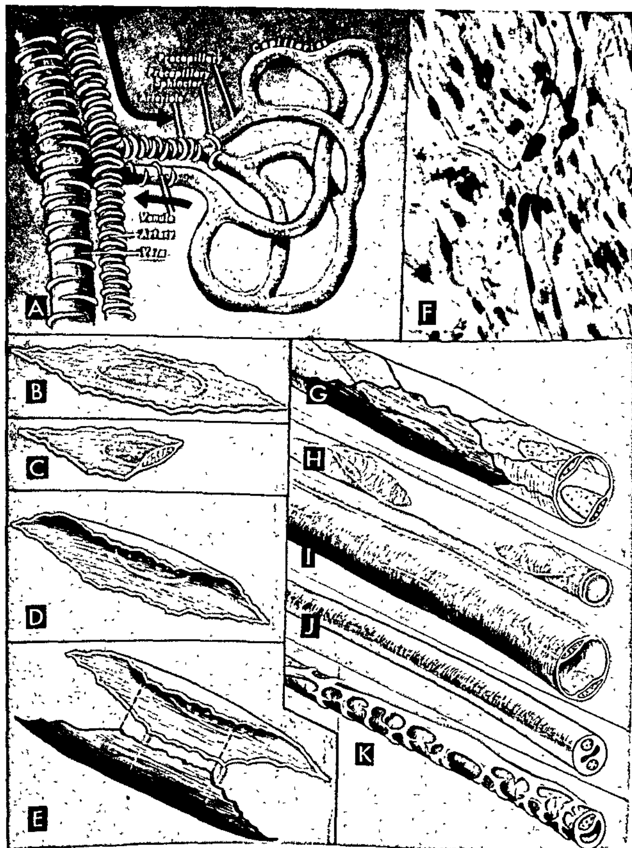


Fig. 1-79. A. Blood is carried through arteries and arterioles into the capillary bed. It returns through venules and veins toward the heart. The artery is narrower than the vein and has more smooth muscle cells in its wall than the vein. B. The endothelial cell is the building stone for capillaries. C. In section, this flat cell shows a bulge around the nucleus. D As part of a tube, it must be curved E. Two endothelial cells fit together, surrounding an average capillary. F. The vertical capillary in this picture is of average caliber. The wall of the extremely thin one at the

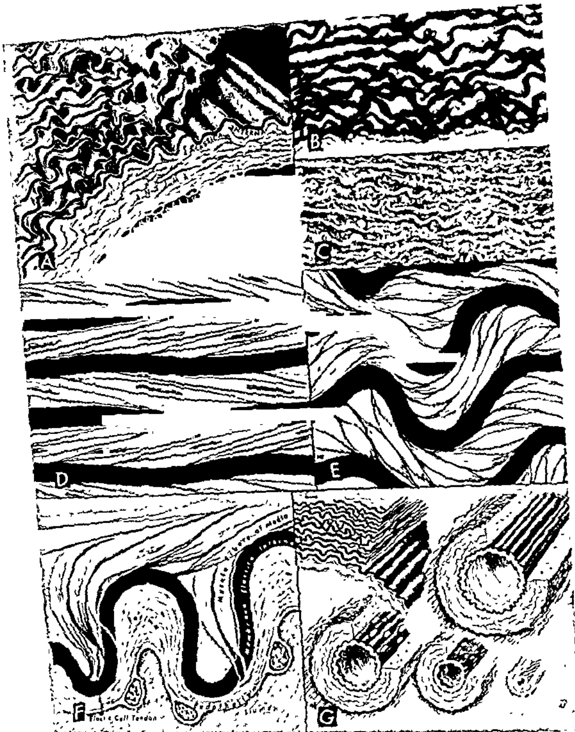


Fig 1-81. A The tunica media of the large, conducting arteries contains many fenestrated, elastic membranes connected by elastic bands The elastica interna is solid B With resorcin-fuchsin, the elastic tissue is stained exclusively (aorta of infant). C Hematoxylin and eosin stains the muscle *cells of the media* The elastic membranes remain unstained and therefore appear as white lines (aorta of infant) D. Smooth muscle cells attached by elastic cell tendons connect the elastic membranes E When the muscle fibers contract, the elastic membranes become wavy, the vessel is narrowed, and the blood pressure increases F. There are two methods of attachment of muscle cells to the *membrana elastica interna* of conducting arteries. G The larger the artery, the more prominent is the *elastic tissue* of its wall The smaller the artery the more prominent is its muscular component (*From Elias*, 1950)

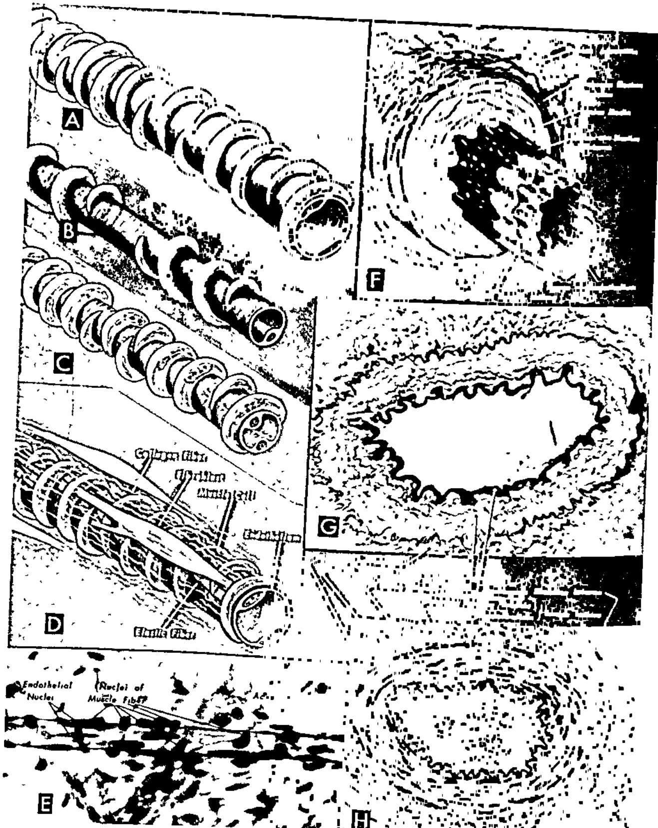


Fig 1-80. A. An arteriole consists of endothelium plus circular, smooth muscle cells forming the tunica media B. One smooth muscle cell may wind around an arteriole several times. C Contraction of the muscle cells causes narrowing of the arteriole D All the layers of a complete blood vessel are present in an arteriole, although they are modestly developed E Endothelial and adventitial nuclei run lengthwise, muscle nuclei, circularly At the edge muscle nuclei are seen head on F, G, H. In medium-sized arteries, the layers characteristic for all blood and lymph vessels are most clearly recognizable (From Elias, 1950)

them are seen here in transverse optical sections Longitudinal nuclei outside the media belong to fibroblasts of the adventitia

Precapillary arterioles (the smallest arterioles) pass the blood from the arterioles to the capillaries. They may be provided with sphincters consisting of a single, smooth muscle cell.

CAPILLARIES

The capillaries branch extensively and form networks whose structure varies with the particular tissue which they supply (Fig 1-79A).

The building stone of the capillary wall is the *endothelial cell*, a flattened, irregular, hexagonal cell (Fig. 1-79B). These cells are curved (Fig. 1-79D) and arranged with their long axis parallel to the longitudinal direction of the capillary. The edges of these cells are wavy, as can be seen in silver-impregnated slides. Two endothelial cells usually fit together to surround an average-sized capillary (Fig 1-79E and G), but a thin capillary may have a *circumference* of one single endothelial cell (Fig 1-79H and F, upper left, and Fig 1-85A, B). Where the *nucleus is located*, the *endothelial cell is thickened* (Fig. 1-79C). The nucleus resembles that of a *fibroblast It is* large and contains small scattered chromatin particles (Fig 1-79C).

It has been claimed (*Chambers and Zweifach*) that intercellular cement, which was said to be instrumental in the *transmission of substance*, exists between the endothelial cells However the ...

... Electron micrograms do *not show* any cement substance in the *extremely narrow* intercellular spaces (Fig 1-85B, *right*).

To *permit* the passage of substances, the cytoplasm of the endothelial cells themselves acts as a semipermeable membrane. Leucocytes and parasitic *organisms bore* through the endothelial *cells*, which close again behind them like temporarily punctured rubber membranes Occasionally, such actively moving bodies may slip through between two endothelial cells.

In the endothelium of the capillaries of the kidney glomerulus and the adrenal cortex, large *pores* are demonstrable with the electronmicroscope (Oberling, Gautier, Bernard, Hall, Pease). Here the endothelium, acting like a simple sieve, permits the passage of large molecules.

The capillary wall is extremely thin (Fig 1-79F and I) and is supported externally by a very thin basement membrane, which requires vitamin P (*rutin*) and vitamin C (*ascorbic acid*) for the maintenance of its pliability. The capillary wall is almost imperceptible in a whole mount. Even when stained, only the nuclei located in this wall are clearly visible In routine preparations, no cell boundaries are seen. The cell boundaries can be made visible with silver nitrate. In cross section, as in Fig. 1-79G, the cut end of a *capillary may appear* as a binucleated ring or as a signet ring (Fig 1-85A, B).

Capillaries, furthermore, can undergo narrowing. When this occurs, the *endothelial cells* become thicker and their *nuclei become cylindrical* (Fig 1-79J), *often projecting into the* lumen of the vessel (*Zweifach*, 1934).

Almost all capillaries are located within the connective tissue The immediately adjacent fibroblasts and connective tissue fibers constitute a primitive tunica adventitia.

The renal glomerulus consists of a highly specialized kind of capillary, *if capillary it can be called* The renal glomerulus actually is a flat, highly branched sheet, lined on both sides by a basement membrane. It is filled by a mass *of cells* which are continuous with the endothelium of the vas afferens and vas efferens and *which therefore* belong to the endothelial system. It appears, however, that they are quite *different* from ordinary endothelium No cell boundaries can be *shown* between them, so that it *can perhaps* be assumed that they are syncytial, and the mass has been called "endenchyma" (*Elias*, 1957) (see Chap 11). In this

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musculature of the *distributing* arteries controls only their caliber It determines the volume of blood admitted to each region and controls the blood *pressure proximately*. F *The* adventitia of tortuous arteries, *like those in the uterus*, contains much elastic ...
...). G This elastic tissue ...
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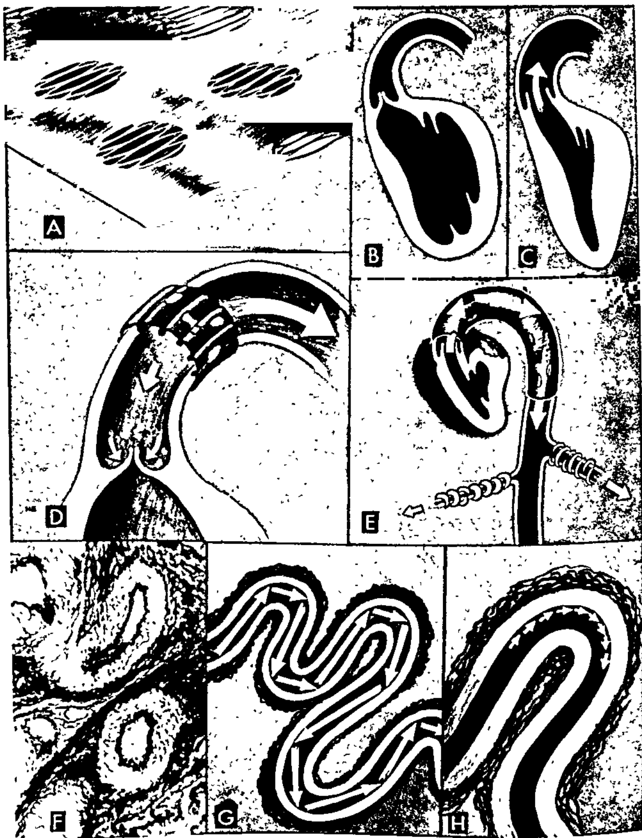


Fig. 1-82. A. The relation of muscles to elastic membranes is best exemplified in the aorta of hoofed animals B During diastole, aorta and pulmonary artery are narrow The semilunar valves are closed. C. Systole forces blood through the semilunar valve The sudden influx of blood expands the conducting artery. D. The elastic membranes rebound and, by their contraction, force most of the blood forward (large arrow). Backward flow (small arrows) closes the semilunar valves. E. The entire energy for blood propulsion is furnished by the ventricular systole. Blood flow toward the periphery is caused by the elasticity of the nonmuscular components of the arterial wall The

mass, blood channels course, which, in all probability, can shift their position from place to place within the endenchyma of the "lamina vasculosa glomeruli" (see Chap 11).

VEINS

The smallest veins (venules) consist of endothelium only, but as they increase in size, they take on the characteristic blood vessel layers which are generally much thinner than in arteries However, in the veins of the extremities (particularly those of the legs, which have to resist a high hydrostatic pressure), the walls are as thick as those of the arteries (Fig 1-83B)

Many veins, especially those in which the blood flows upward, are provided at intervals with *valves* These are flaps or cusps, oriented so that as the blood flows toward the heart, they are pushed against the wall, permitting the blood to flow without obstruction (Fig. 1-83D). However, if blood flow is reversed, the weight of the blood and pressure of the surrounding tissues cause the blood to fill the pockets of the valve and the flaps close, as a drawbridge, occluding the lumen and making backflow impossible (Fig 1-83C).

The valves are projections of the tunica intima On the side directed against the blood flow, each flap consists of a network of elastic fibers which is continuous with the membrana elastica interna of the vein The side of the valve facing the wall of the vein is relatively free of elastic fibers. The space behind it is called the *sinus* of the valve, and here the wall of the vein is usually distended and thin (Fig. 1-83B)

The large veins in the abdomen, such as the inferior vena cava, the renal, and suprarenal *veins*, lack circular muscles in the tunica media They are characterized by strong, longitudinal musculature in their adventitia, also by numerous longitudinal, elastic fibers in the same layer. This longitudinal *reinforcement* keeps these vessels patent against lateral, intraabdominal pressure.

COMPARISON OF ARTERIES AND VEINS

There is ideally a 1:1 ratio between the number of *arteries* and veins in the body, with a corresponding vein for every artery This means that a given *region is* supplied by a specific artery and drained by a specific vein However, for the very small vessels, the number of veins is often twice that of arteries, a small artery often being accompanied by two small veins. The suprarenal gland, on the other

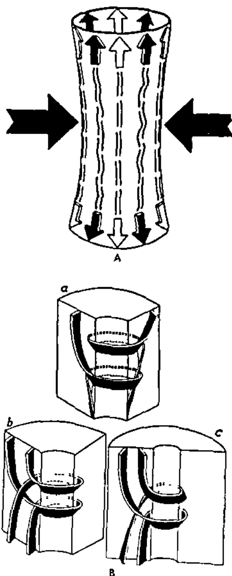


Fig 1-84. A. The longitudinal muscle fibers (symbolized by white *arrows)* and the longitudinal elastic fibers (black arrows) in the adventitia of the vena cava inferior and venae suprarenales provide strong longitudinal *traction* capable of counteracting the transverse pressure of the viscera, which would otherwise cause the collapse of *this vessel B* a, Polar arrangement of fiber bundles (crossing bundles), b, bundles running in the same general direction; c, irregular *course of* fiber bundles (From Fischer, *modified after Goerttler.)*

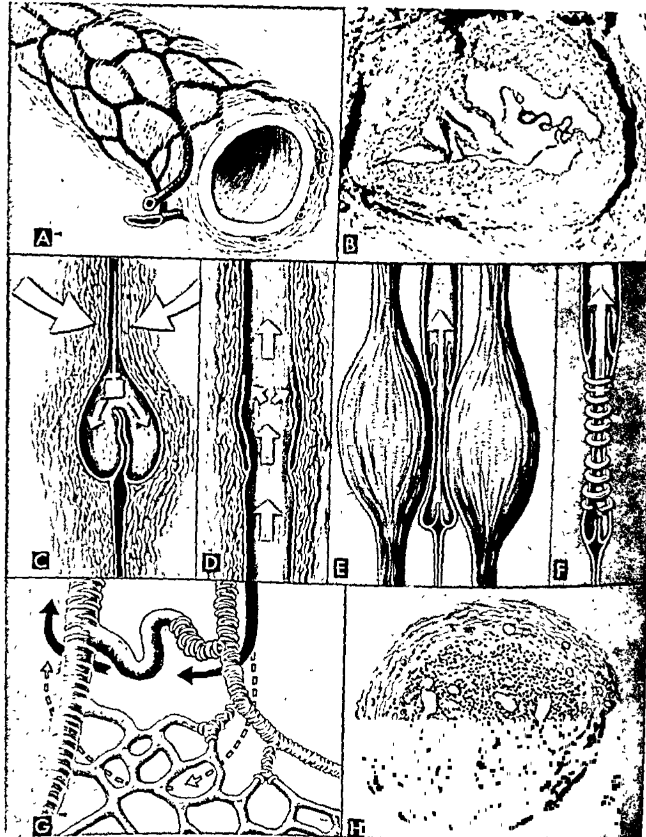


Fig 1-83. A. The walls of larger blood vessels receive blood supply through plexuses of small vessels, the *vasa vasorum*. (*From Elias Dental Digest, 1950*) B This is a cross section, passing through a valve consisting of two cusps of a thick-walled vein in an extremity Thick walls help these veins to resist hydrostatic pressure C The weight of the blood and pressure of the surrounding tissues cause the blood to fill the pockets of the valve cusps and thus make backflow impossible. D When blood is flowing toward the heart, the valves are opened. E Blood propulsion in the veins of the extremities is aided by contractions of surrounding muscles F Contractions of the smooth musculature in the media of these thick-walled veins probably contribute to the upward movement of blood G. Blood may bypass the capillary bed through an arteriovenous anastomosis, *AVA*, when capillaries are closed by precapillary sphincters and AVA sphincter is open. H. Some arteries end in a highly convoluted nodule, called glomus, in which the muscle fibers are transformed into epithelioid cells. (*Redrawn after Staubesand, 1953*)

blood enters the organ on one side and emerges on the opposite side.

ARTERIOVENOUS ANASTOMOSES

Arteriovenous anastomoses (AVA) exist in many parts of the body. They are side branches which arise from arteries (Fig 1-83G), bypass the capillaries, and transport blood directly to the veins. They are often tortuous The histologic transition from the arterial to the venous part of an AVA is sudden and may be seen as a change from an arterial vessel with a thick muscular media to a venous, thin-walled vessel.

The precapillary sphincters and the media of the arterial part of the AVA (Fig 1-83G) regulate the blood supply and the temperature of the region If the AVA are dilated, greater amounts of blood will flow through a region, maintaining body temperature when extremities are subject to cold, and may also increase venous blood pressure to aid the return of blood to the heart.

GLOMUS ORGANS

Some arteries end in a highly convoluted nodule, called a glomus (Fig 1-83H). They are extremely tortuous and sometimes branched The muscle fibers of such a glomus (or skein) are modified and have undergone a transition into epithelioid cells Staubesand (1953) has given an excellent account of arteriovenous anastomoses. The tunica media of neighboring windings may fuse so that the glomus becomes a solid mass of epithelioid cells tunneled by the branches of the AVA

Visceral afferent and sympathetic innervation points to a possible sensory and endocrine function of the glomus organs

hand, is supplied by a great number of arteries and a single vein.

The larger the territory supplied or drained, the larger the vessel. Therefore, very large veins are relatively far from their corresponding arteries, whereas the smaller vessels run, in general, close to each other, though in opposite directions. In endocrine glands and in the liver,

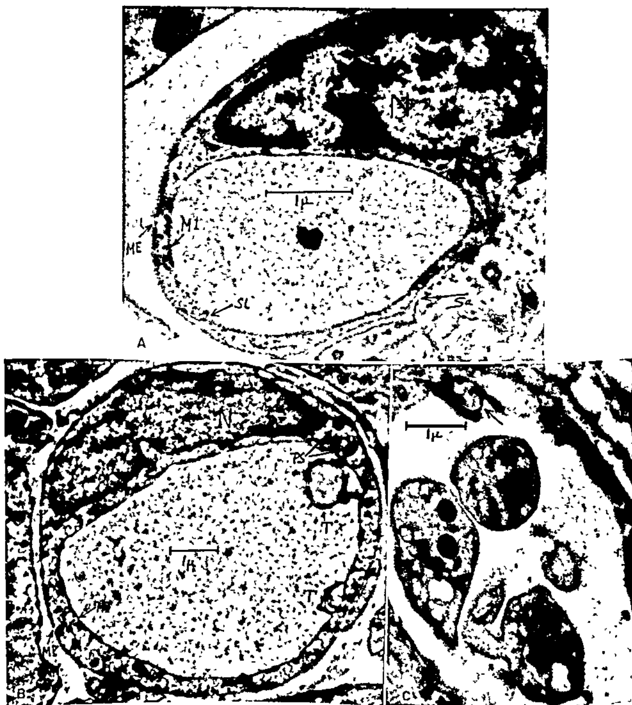


Fig. 1-85. A. Capillary from the atrium of a normal guinea pig N, nucleus; MI, membrana interna; ME, membrana externa; SL, slit in the wall of the capillary; PS, plasmasomes; Sa, sarcolemma of neighboring muscle fiber. Original magnification ×4,600. (*Courtesy of B Kisch.*) B. Capillary in the atrium of a guinea pig. Initials as in (A) T, fine tentacles reaching into the blood stream in the capillary. Between the two lower tentacles a slit in the capillary wall can be seen. (*From B. Kisch and G. Martin, courtesy of the authors*) C Three blood platelets in a pulmonary capillary of a normal mouse. Asterisk indicates another blood platelet Each of them has a membrane and in a light matrix some osmiophylic enclosures and small vacuoles. The arrow points to a slit in the wall of the capillary. (*From B. Kisch, courtesy of the author.*)

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The larger the territory supplied or drained, the larger the vessel Therefore, very large veins are relatively far from their corresponding arteries, whereas the smaller vessels run, in general, close to each other, though in opposite directions. In endocrine glands and in the liver,

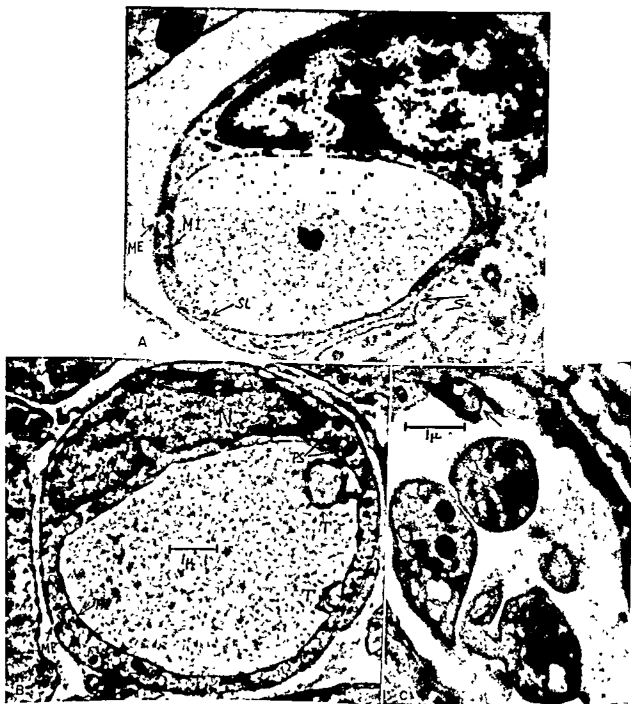


Fig 1-85. A Capillary from the atrium of a normal guinea pig. *N*, nucleus; *MI*, membrana interna; *ME*, membrana externa; *SL*, slit in the wall of the capillary, *PS*, plasmosomes; *Sa*, sarcolemma of neighboring muscle fiber. Original magnification ×4,600 (*Courtesy of B Kisch.*) B. Capillary in the atrium of a guinea pig Initials as in (A) *T*, fine tentacles reaching into the blood stream in the capillary. Between the two lower tentacles a slit in the capillary wall can be seen. (*From B. Kisch and G. Martin, courtesy of the authors*) C Three blood platelets in a pulmonary capillary of a normal mouse. Asterisk indicates another blood platelet Each of them has a membrane and in a light matrix some osmiophylic enclosures and small vacuoles The arrow points to a slit in the wall of the capillary. (*From B. Kisch, courtesy of the author.*)

fashion and then interconnecting to form the [illegible] This concept [illegible]

[illegible] role, not unlike a system [illegible] subservient to changes in the large muscular channels feeding and draining the network.

Reconstructions, based on direct observational studies of the circulation in different tissues, have led to the recognition of certain architectural features Perhaps the least complicated version of the capillary bed is encountered in the mesentery, where the original observations on the *preferential channel* concept were made (Zweifach, 1937). Upon entering the tissue which they are to supply with blood, the small arteries subdivide several times in the conventional manner into progressively narrower units until vessels approximately 20 to 30 μ in diameter are formed These are the so-called *terminal arterioles*, which consist of an inner endothelial lining closely invested by a clearly evident, thin layer of smooth muscle Despite the fact that the direct continuations of the arterioles within the capillary bed proper undergo a progressive change in their structural make-up, the vessel can be readily recognized almost to the venous side This portion of the arteriolar tree is an extraordinarily thin, straight vessel with numerous offshoots spilling blood into the capillary network. The offshoots arise abruptly as narrow *side branches* of the parent trunk and are frequently coiled. The centrally placed parent stem shows a progressive loss of its investment of smooth muscle. During this transition, the muscle elements become at first spaced at irregular intervals and then are transformed into atypical, thin perivascular cells, which are increasingly difficult to recognize in the living state. The muscle cells are somewhat more [illegible]

fur[illegible]

for[illegible]

[illegible] terminates Beyond this, the offshoots continue as *nonmuscular capillaries* with occasional histiocytic or other mesenchymal elements applied to the outer wall The greatest number of side branches is given off in the region where the arteriolar extensions are about 15 to 20 μ in diameter As in the case of the larger arterioles, these side branches can be shown to have smooth muscle only in the immediate junctional region. These circumstances, the abrupt angle of branching and the restriction of muscle to the region of bifurcation, create a unique structural element, to which the term *precapillary sphincter* has been applied Their strategic location enables these structures to regulate the amount of blood entering the capillary vessels.

The major portion of the capillary network is therefore made up of *simple endothelial tubes* which show no evidence of perivascular muscle The distal extensions of the arteriolar trunk also become progressively less muscular until ultimately they are morphologically indistinguishable from the true capillaries. Even in this region, the vessel continues to give off capillary side branches However, since the parent vessel contains no obvious muscle, the branches likewise are devoid of such elements.

TERMINOLOGY

With the above background, it is possible to define the terms used to describe this portion of the circulatory tree

Capillary Bed. The term was originally used in a loose manner to designate the network of vessels across which blood tissue exchange occurs. Others have accepted the term as referring to all the microscopic vessels within the tissue proper concerned with the local distribution of the blood. In this regard, the term is synonymous with "terminal vascular bed" or "peripheral vascular bed." Sir Thomas Lewis was aware of the need for a more critical approach to this area of the circulation, and preferred to use the term "minute blood vessels," because of the difficulty in identifying the elements concerned, even in a readily accessible structure such as the skin In the present discussion, the terms *capillary bed* and *terminal vascular bed* are used interchangeably.

Capillary. Considerable difficulty is encountered in determining from microcirculatory studies in the literature the type of vessel under discussion, since in many instances identification is based almost exclusively on caliber alone Frequently, as in the case of skin studies, where the width of the circulating column of blood served as the means of identification, reference is made to capillaries 20 to 40 μ in diameter. Actually, the capillaries in particular species are slightly larger than the red blood cells, so that they average in caliber from 10 to 15 μ in mammals and from 20 to 30 μ in most amphibia Preferred usage of the term *capillary* restricts it to endothelial channels possessing

I

The structural basis of the microcirculation

B. W. ZWEIFACH

The relative inaccessibility of the extreme peripheral portion of the vascular tree has frequently made it more the object of speculation than of direct investigation and given rise to rather vague notions of the structural organization of this area. Although detailed knowledge exists concerning particular constituents of the capillary system in different tissues, comparatively few studies have attempted to reconstruct this scattered information into a working model of the capillary bed as an organic entity. Out of the work of such pioneers as Krogh, Dale and Richards, Clark and Clark, and Lewis has come the realization that the intrinsic activity of the microscopic vessels controls the distribution of blood to the tissues independently of the systemic circulation This concept has brought into usage the term *capillary bed* as a means of referring to the *collective behavior of the minutiae of the peripheral vascular apparatus, the terminal arterioles, precapillaries, capillaries, and venules* As will be indicated below, the validity of such a concept is strongly supported by structural considerations.

The term *capilla* was originally used in a general sense to designate all the exceedingly fine, hairlike terminations of the arterial system, visible only under the microscope Subsequent application of the term has failed to take account of the fact that not all the vessels of capillary dimensions are structurally similar Careful study reveals that the microscopic vessels are not distributed haphazardly, as was thought to be the case for many years, but are laid down in recognizable patterns which follow several fundamental prototypes In essence, the structural framework of the capillary bed consists of a centrally placed *parent stem*, which follows a relatively straight course and from which are distributed large numbers of *side branches* as the trunk spreads out peripherally In the peripheral reaches of the bed, the parent arterial stem becomes almost indistinguishable from the surrounding network of capillary side branches. The earliest manifestations of the venous system arise in direct relation to the *terminal ends* of the central parent stem

Although it is readily apparent from the literature that the capillary beds in different tissues do *not* have an identical pattern of organization, each of these systems possesses certain common structural and functional features which are the basis of its physiologic activities. Modifications exist in the relative number of the different types of vessels, the extent of interanastomosis between arterial and venous vessels, and peculiarities introduced by the architecture of the parenchymal structures being supplied with blood

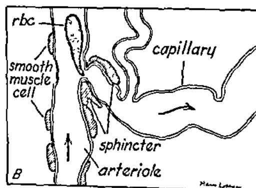
Little significance has been attached in the past to the manner of branching of the arterial tree within the tissue proper, the assumption being made that with each successive division, the vessels simply became narrower until they were in effect capillaries The capillaries themselves were depicted as branching in random

rioles (mesentery, bladder, skeletal muscle) or by the fusion of converging postcapillaries (cheek pouch, skeletal muscle, skin). The vessels rapidly acquire a well-defined connective tissue coat The collecting venules, like the true capillaries, are nonmuscular and show only minor changes in caliber secondary to fluctuations in blood flow. It is only after venules of the order of 50 to 75 μ have been formed that the vessels begin to show smooth muscle cells in their walls, at first irregularly distributed and later as a circular layer. The muscular venules under normal circumstances exhibit no spontaneous vasomotion and are poorly reactive to vasoconstrictor influences The collecting venules are the least distensible constituents of the microcirculation, whereas the muscular venules show a considerable range of variations in caliber, particularly during periods of hyperemia

STRUCTURAL MODIFICATIONS IN SMALL BLOOD VESSELS

During the structural transition of arteries into arterioles, and thence into the microcirculation, a number of changes occurs in the make-up of these vessels and their relationship to the parenchymal elements, which have important consequences for their functional properties. As the arteries diminish in size, the muscle coat thins to a single layer, and the connective tissue constituents, particularly the elastic fibers, diminish until they are only a minor constituent. The distensibility of the large blood vessels is in major part a property of the elastic fibers and thus is governed by







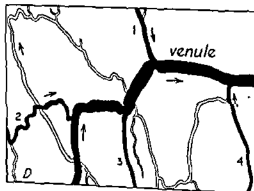


Fig 1-86. A, B Circulation in mesoappendix of rat showing a precapillary sphincter during the constrictor phase of the vasomotor cycle As indicated in (B), the parent arteriole ... narrowed while only the junctional neck of th... [illegible]

... the wall of the collecting venules is thickened, chiefly because of a layer of connective tissue. ... directions. None of the tributaries is ... X42

no discernible perivascular components. The consensus of opinion (Clark and Clark; Fulton; Illig) is that the capillaries do not possess contractile elements. Vessels of capillary dimensions with muscular components have been described, but they are considered as part of the arteriolar system.

Terminal Arteriole. The term is used for the most part in a descriptive sense to refer to the ramifications of the arterial tree (30 to 50 μ in diameter) which possess a conspicuous, single layer of smooth muscle. Unfortunately, the direct extensions of the arterioles progressively lose their structural characteristics, so that they merge almost imperceptibly with the capillary vessels Many authors (Nicoll and Webb, Grafflin and Bagley) prefer to use *terminal arteriole* to designate the entire muscular channel, even though its end point is difficult to establish The author (see Chambers and Zweifach, 1944) suggested restricting the term *terminal arteriole* to the point where the vessel begins to distribute capillary side branches. Although the vessel follows a variable course in different tissues beyond this point, its pattern of branching is sufficiently uniform and striking to serve as an identifying characteristic The term *metarteriole* was assigned to the remainder of the arterial segment within the capillary bed proper The distinction is of more than academic interest, since the relative importance of neurogenic and humoral agents in the regulation of blood flow, reactivity thresholds, and the influence of local tissue factors differs in these two segments of the arterial system

Metarteriole. The prefix *meta*, meaning "beyond," refers to the final segment of the terminal arterioles within the capillary bed proper from which the capillaries are in the main distributed. These vessels, which usually have the same diameter as the capillaries, possess thin, closely adherent smooth muscle cells spaced at irregular intervals Eventually, the elongated, spindle-shaped smooth muscle cells, characteristic of the arterial system, are no longer seen Some question exists whether branched smooth muscle cells (Rouget) are present, representing a poorly differentiated prototype of the spindle-shaped elements encircling larger vessels. There is no conclusive evidence that these atypical cells can act as contractile elements. These vessels have also been referred to as *precapillary arterioles*, identification being made primarily by virtue of the large number of precapillary branches.

Precapillary Sphincter. The majority of capillaries originate as branches which leave the parent stem of the arterioles and metarterioles at an abrupt angle and possess an investment of smooth muscle for a variable but limited distance. This junctional segment of the capillary offshoot, referred to as the precapillary sphincter (Fig. 1-86A, B), continuously displays vasomotor changes which interrupt the flow of blood into the capillaries independently of changes in the parent stem. The precapillary muscle cells, as shown by Jones (1936) and by Webb and Nicoll, may coil several times about the branch, so that even slight contraction narrows the orifice in the sphincter region sufficiently to prevent entrance of the formed elements of the blood, and at times allows only plasma to enter. The patency of the sphincter orifice at any particular moment varies in different vessels and regions depending upon the state of tone of the smooth muscle. During vasomotor excursions, the precapillary sphincters usually open or shut completely. Various investigators, including Tannenberg and Sanders et al., have described narrowing of bifurcations of what appear to be precapillary vessels induced by the swelling of perivascular cells. It is probable that the wide range of changes in precapillary vasomotion represents several fundamentally different processes, including this form of cellular "swelling," temporary lodging of leucocytes at points of branching, etc.

Postcapillary. As the capillaries course distally, they are joined by other capillaries to form wider (15 to 20 μ) vessels, referred to as postcapillaries. In some tissues, such as the undersurface of the skin and the intestinal wall, these channels are quite prominent and extensive The vessels have a recognizable connective tissue sheath and are the sites where extravasation of blood cells occurs most frequently (Lutz et al , Lee et al.).

Collecting Venule. As the term implies, these vessels (30 to 50 μ wide) form the effluent channels of the capillary bed (Fig 1-86C, D). They originate in several ways; frequently, either as direct continuations of the metarte-

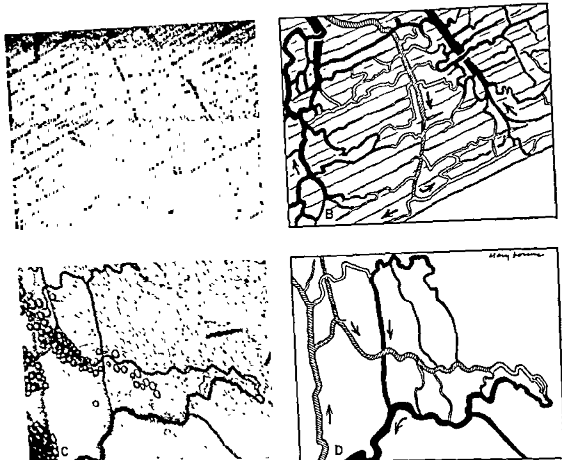


Fig 1-87. A, B Circulation in transilluminated sheet of skeletal muscle (spinotrapezius muscle of rat) The structural units of the tissue, the individual muscle fibers (about 100 μ wide), are clearly visible The preferential channel (cross-hatched in center of drawing) distributes at least one capillary branch to each muscle fiber The majority of capillaries in this preparation are closed down Note that flow continues to distal end of preferential channel, where vessel bifurcates and after a short course turns back as a collecting venule (solid black) Most of precapillary vessels, as they leave central vessel, possess muscular sphincters $\times 60$ C, D Simplified version of preferential channel seen in mesorchium of rat As indicated in tracing at right, metarteriole (cross-hatched) distributes several capillary branches, only two of which are active, before turning on its course and forming a collecting venule (solid black) $\times 42$.

the edges, the metarterioles form anatomically distinct, preferential channels which serve as the major tributaries of the venous system for the skeletal muscle circulation.

ARTERIOVENOUS SHUNTS

The literature contains frequent references, chiefly on the basis of indirect measurements of flow, that shunts exist between the arterial and venous circulation so as to bypass the extensive network of capillaries (Barcroft and Swan) Such arteriovenous shunts have been described in tissues such as the skin (Clara) and wall of the gastrointestinal tract (Barlow) Occasional direct connections between the microscopic arterioles and venules can be seen in the mesentery, omentum, and bladder (Zweifach, 1949). Arteriolar-venular shunts are consistently present in the interfascicular connective tissue layers of skeletal muscle bundles, although even here they constitute a comparatively small fraction of the population The microcirculation in skeletal muscle differs from other tissues in another respect by being supplied through short branches from arterioles as large as 75 μ in diameter These vessels divide only once or twice and run only a short course before they rejoin the venous circulation Although not shunts in a morphologic sense, such branches effectively divert blood back to the

purely physical laws (Burton). On the other hand, the walls of the terminal arterioles, metarterioles, and precapillary sphincters consist chiefly of smooth muscle, so that their compliance to pressure changes is determined by the tone of the smooth muscle elements, a variable factor subject to intrinsic regulation (Folkow).

Up to this point, the components of the arterial system are discrete, independent structures. In the microcirculation, the vessels, being no longer insulated by a connective tissue coat, are directly embedded in the general ground substance and become an integral part of the tissues. This circumstance brings the vessels into intimate contact with the chemical milieu of the tissues, and thereby exposes the microcirculation to a new set of regulatory influences, the local tissue hormones In view of the comparatively sparse sympathetic innervation, local chemical influences become of prime importance in the regulation of the microcirculation.

There are several important consequences of the exposure of the smooth muscle elements in the terminal vascular bed to the tissue milieu. This circumstance provides a means whereby local factors can modulate and even override centrally mediated impulses, since they intervene at the effector unit directly Furthermore, inasmuch as the smooth muscle elements are more reactive to vasoconstrictor and dilator agents, their activities now show a considerable degree of independence from the rest of the circulation.

CAPILLARY PATTERNS

The final ramifications of the metarterioles join the venous side of the bed in one of three ways. The vessels may continue as *preferential channels* which are then joined by adjacent capillaries to form a collecting venule In other instances, the vessel continues as a preferential channel for the greater part of its course and then *bifurcates* into several branches in close proximity to a venule before joining that structure. In structures where the terminal vascular bed is spread out over an extensive surface, the terminal arterioles *interdigitate* with one another to form a series of arcuate vessels. Metarteriolar-type vessels then come off at right angles from the arteriolar arcades to form the capillary bed proper.

Modifications of the schematized architectural pattern can best be described in relation to the tissues in which they occur. Preferential or thoroughfare channels in the capillary circulation were originally described in various mesenteric appendages of mammalian and cold-blooded laboratory animals (Chambers and Zweifach, 1946). A similar structural arrangement is seen to a limited degree in the wall of the small intestine, in the undersurface of the skin, and along the free edges of skeletal muscle. Figure 1-87 shows a simplified version of this type of vascular architecture in a mesenteric appendage (Fig. 1-87C, D), and a more complex modification of the preferential channel pattern in skeletal muscle (Fig. 1-87A, B). In a hollow viscus, such as the gut or the urinary bladder, many of the arterioles (15 to 20 μ) turn and continue as venous structures before losing completely their muscular coat

Observations on the circulation in loose connective tissue, such as that in the fascial layers of the body musculature, in the hamster cheek pouch, in glandular structures such as the pancreas, and in the surface of the urinary bladder, reveal that many metarterioles do not continue to the venous circulation as morphologically distinct preferential channels. However, even here, the arrangement of the precapillary side branches is such as to enable the parent trunk to penetrate into the very center of the capillary system and, under conditions of partial vasoconstriction, to continue to perfuse blood only through the metarteriole and its most terminal branches Two examples of this type of vascular arrangement are visible in the hamster cheek pouch and in the subcutaneous tissue of the rabbit (Fig 1-88)

The *arcuate pattern* of distribution, involving both arterioles and venules, is striking in skeletal muscle (Fig. 1-89) and in the wall of the intestinal tract. Arcuate vessels, particularly between arterioles, are present to a more limited extent in the hamster cheek pouch, and to some extent in parenchymatous tissues. The interdigitations of the arterioles block off small areas of tissue which are then supplied by metarteriolar branches distributed by the arcuate vessels so as to approach the center of the tissue mass from several directions In the depth of the skeletal muscle tissue, the final arterial twigs simply lose their identity after distributing 5 to 10 capillary branches Along

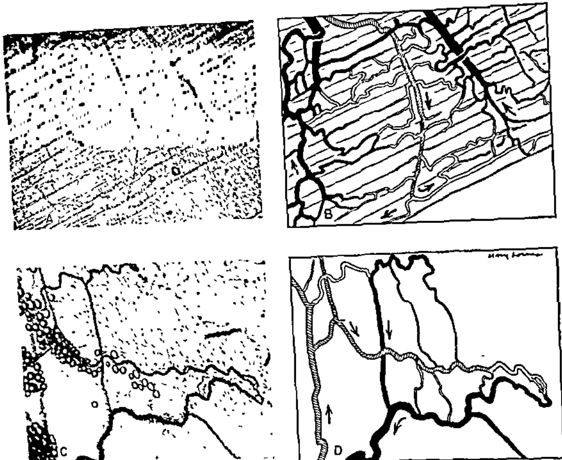
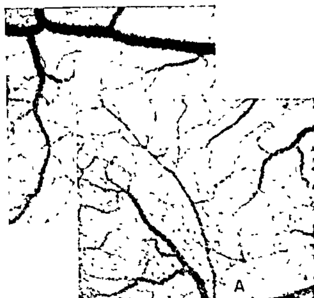


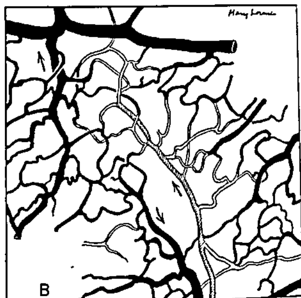
Fig. 1-87. A, B. Circulation in transilluminated sheet of skeletal muscle (spinotrapezius muscle of rat) The structural units of the tissue, the individual muscle fibers (about 100 μ wide), are clearly visible The preferential channel (cross-hatched in center of drawing) distributes at least one capillary branch to each muscle fiber. The majority of capillaries in this preparation are closed down Note that flow continues to distal end of preferential channel, where vessel bifurcates and after a short course turns back as a collecting venule (solid black) Most of precapillary vessels, as they leave central vessel, possess muscular sphincters ×60 C, D. Simplified version of preferential channel seen in mesorchium of rat As indicated in tracing at right, metarteriole (cross-hatched) distributes several capillary branches, only two of which are active, before turning on its course and forming a collecting venule (solid black) ×42.

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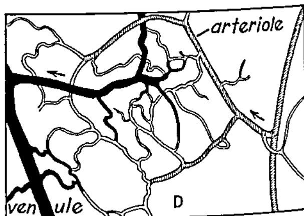


Fig. 1-88. A, B. Capillary circulation with a functional type of preferential channel as exemplified by photograph of bed in cheek pouch of the hamster. The distal continuation of the arteriole (cross-hatched in tracing) is readily visible to point of final branching just before vessel approaches collecting venules (solid black) ×60. C, D Conventional network of capillary vessels as seen in mesentery of rabbit There is no evidence (structural or functional) of preferential channels Sphincters are present in branches of cross-hatched arteriole but not at terminal bifurcations. ×60.

venous side even when the remainder of the capillary circulation to the muscle proper has been drastically diminished, as during hemorrhagic shock

TRUE CAPILLARIES

The several structural elements which make up the capillary wall deserve special comment The *endothelial cell* is the component to which most investigators ascribe the functional properties of the capillary wall The cell is characterized by its extreme thinness, although in partially narrowed arterioles or venules, the endothelium appears as rounded cells which are attached along their base and sides and protrude into the vascular lumen. The cytoplasm has an amorphous granular appearance, and has been shown to contain unusual amounts of chemical constituents, such as glycogen and alkaline phosphatase In order to account for the unselective nature of its permeability characteristics, it has been postulated that the endothelial cell represents an atypical, modified cellular entity Histochemical studies of the oxidation-reduction activities of vascular endothelium (Cascarano and Zweifach) do not support this assumption, no major differences being demonstrated between the behavior of these cells and other parenchymal elements

Normally, the cell presents a smooth inner surface which is nonadhesive and which apparently is coated with a thin layer of one of the plasma protein constituents (Zweifach, 1955). Several workers have suggested that the inner lining is fibrinogen (Danielli and Stock) or some closely related substance. The endothelial

vessel in the mammalian capillary bed varies in diameter from about 8 to 15 μ. The capillary tubes are of uniform size, although they tend to become slightly wider as they approach their venous terminations.

The *capillary tube* on the average is made up of from three to four endothelial cells in its circumference On the venous side, the capillary wall contains as many as four to six endothelial cells The cells are joined along their contiguous borders by what appears to be a cement substance, although the precise forces which maintain the intercellular relationship are not completely understood On the basis of the effects of changes in pH and in calcium content (Chambers and Zweifach, 1947), it was postulated that a calcium proteinate served as the cement material for binding the endothelial cells together. Such a cement material has been difficult to demonstrate by electron microscopy and by conventional staining methods Other workers (Linzbach and Hort) have shown the existence of *intercellular bridges* between adjacent endothelial cells in close juxtaposition A considerable body of evidence indicates that the integrity of the endothelial binding, irrespective of whether this is a function of a cement material or of unknown chemical forces, is an important determinant of the permeability characteristics of the capillary barrier.

Another important constituent of the capillary wall is the amorphous condensation of ground substance and fine reticular fibers which surrounds the vessel and forms the so-called *pericapillary sheath* (Volterra). This layer has many of the characteristics of basement membranes in general, although, unlike the latter, it is not appreciably influenced by the absence of calcium in the medium. The pericapillary sheath not only supports the endothelial tube but contributes to its permeability characteristics, particularly with respect to the extravasation of blood cells. The collecting venules, which have the most prominent perivascular sheath, are the most pervious of the capillary vessels. It is interesting to note that the venules are unusually susceptible to local tissue injury, as evidenced by the predilection of these vessels to petechial hemorrhages and stasis following x-ray therapy, vitamin C deficiency, bacterial endotoxins, and other similar conditions.

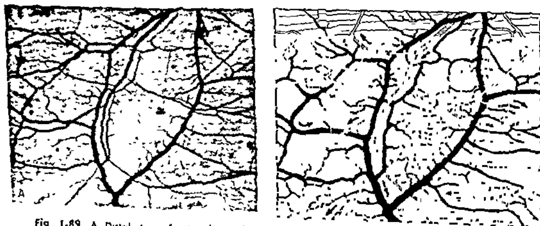


Fig 1-89 A. Distribution of *arterioles* and venules in skeletal muscle preparation (rat) showing
arcuate type of interconnections between these vessels. Note how interarcading arterioles block
off an area in center of photograph which is then supplied by slender metarteriolar type of
vessel B As indicated in tracing, metarteriole loses its identity in center of tissue. Note extensive
network of true capillaries parallel to direction of muscle fibers Venules (solid black) also inter-
connect freely. ×42

14

The innervation of the heart and vessels

G. A. G. MITCHELL

The *autonomic nervous system* regulates cardiovascular, respiratory, alimentary, and other visceral functions, being closely associated in these activities with certain endocrine glands. The control of autonomic functions is essentially involuntary, although influenced by "centers" located at all levels in the central nervous system These so-called centers exist in the premotor and orbital areas of the frontal lobes of the cerebrum, the cingulate gyri, the anterior parts of the temporal lobes, the hippocampi, the anterior and medial thalamic nuclei, the hypothalamus (which includes the hypophysis cerebri), the anterior lobe of the cerebellum, various cranial nerve nuclei and other nuclei in the brain stem, and in groups of neurons in the spinal cord such as those in the lateral gray columns These structurally scattered centers are interconnected by associative, commissural, and projection pathways, with overlapping of autonomic, somatic, and other areas; this explains the common interrelationships between autonomic, somatic, mental, and emotional states Cardiovascular control is one of the most widely represented of all autonomic functions, and changes of the heart rate and blood pressure have been recorded following stimulation, ablation, or injury of every part of the brain and cord mentioned above, although some parts, such as the hypothalamus and certain "vital centers" in the medulla oblongata, are more important than others

The peripheral parts of the autonomic nervous system consists of two paravertebral sympathetic ganglionated trunks; various prevertebral and visceral nerve plexuses (such as the cardiac, celiac, and hypogastric, and their branches), the parasympathetic cranial and pelvic splanchnic nerves; and autonomic fibers which are inherent constituents of most of the cerebrospinal nerves.

Visceral activity of a kind can occur through autonomic pathways independent of the brain and cord, but the complex coordination required, for example, for homeostasis, necessitates an overriding direction by higher autonomic and somatic centers operating in integrated harmony *Autonomic reflex arcs* are constructed from afferent, intercalary, and efferent neurons and resemble their somatic counterparts, except that the outgoing pathway is interrupted by a synapse in a peripheral ganglion, so that *preganglionic* and *postganglionic* elements are described, whereas there are no peripheral synapses in the somatic outflow. There is no fundamental disparity, however, but merely a difference in the location of the autonomic efferent cells which migrate outwards from the developing neural tube to form peripheral ganglionic masses such as those associated with certain parasympathetic cranial nerves and those of the sympathetic ganglionated trunks and prevertebral plexuses. These are the efferent autonomic cells, and, to maintain structural and functional relationships, the intercalary (preganglionic) axons follow these

cells to form synapses with the efferent cells in the ganglia the axons of the latter are the postganglionic fibers

Most of the *preganglionic sympathetic fibers* are the axons of cells in the lateral gray columns of the cord in the thoracolumbar region, and the approximate levels of segmental representation are shown in Fig 1-90. These fibers emerge through corresponding ventral nerve roots and soon leave the spinal nerves in *white rami communicantes* to pass to adjacent paravertebral ganglia Some form synapses with cells in these ganglia, and the axons of these cells rejoin the spinal nerve through *gray rami communicantes* A proportion, especially in the lower cervical and lumbar regions, relay in *intermediate ganglia* (Fig 1-93) on the course of the rami, these ganglia often escape removal in routine paravertebral sympathectomies, this explains some of the disappointing results following these operations. Other preganglionic fibers, e g , those for the upper and lower parts of the body, ascend or descend in the paravertebral sympathetic trunks to relay in higher or lower ganglia in the chains (Fig 1-92). Still others pass uninterruptedly through the paravertebral trunks into their medially directed branches and so reach and relay in ganglia in the prevertebral plexuses (cardiac, celiac, hypogastric, etc). The axons of these ganglionic cells, the postganglionic fibers, are distributed with the spinal nerves and in vascular and visceral branches of the sympathetic trunks and prevertebral plexuses They are concerned with the control of cardiac, vasomotor, secretomotor, and other functions. In general, sympathetic efferent activity is associated with cardiac acceleration and vasoconstriction, although there are exceptions to this. The *afferents* convey cardiac and vascular stimuli which produce appropriate modifications in the efferent impulses

The *parasympathetic outflow* is reputedly limited to the cranial and caudal ends of the neuraxis. There is some inconclusive evidence, however, of an outflow of vasodilator fibers through the dorsal roots of the spinal nerves; *unless these exist, there is no known parasympathetic supply to the vessels of the parietes and limbs* (Mitchell, 1953, 1956).

Parasympathetic fibers are found in the third, fifth, seventh, ninth, tenth, and eleventh cranial nerves, and in the pelvic splanchnic nerves As in the sympathetic component, some fibers are efferent in type and others afferent, e g , many sensory fibers from vascular and visceral structures are carried in the fifth, ninth, and tenth cranial nerves The cranial preganglionic fibers in the third, seventh, and ninth nerves relay in the ciliary, otic, sphenopalatine, and submandibular ganglia and perhaps in other small ganglia alongside the carotid, facial, pharyngeal, and other arteries (Lazorthes, 1949). Those emerging in the *glossopharyngeo-vago-accessory complex of nerves* mainly relay *in the* cardiac, pulmonary, celiac, enteric,

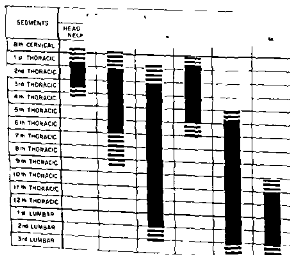


Fig 1-90 Approximate segm... the preganglionic outflows, ... or caudally in association

14

The innervation of the heart and vessels

G. A. G. MITCHELL

The *autonomic nervous system* regulates cardiovascular, respiratory, alimentary, and other visceral functions, being closely associated in these activities with certain endocrine glands. The control of autonomic functions is essentially involuntary, although influenced by "centers" located at all levels in the central nervous system. These so-called centers exist in the premotor and orbital areas of the frontal lobes of the cerebrum, the cingulate gyri, the anterior parts of the temporal lobes, the hippocampi, the anterior and medial thalamic nuclei, the hypothalamus (which includes the hypophysis cerebri), the anterior lobe of the cerebellum, various cranial nerve nuclei and other nuclei in the brain stem, and in groups of neurons in the spinal cord such as those in the lateral gray columns These structurally scattered centers are interconnected by associative, commissural, and projection pathways, with overlapping of autonomic, somatic, and other areas; this explains the common interrelationships between autonomic, somatic, mental, and emotional states Cardiovascular control is one of the most widely represented of all autonomic functions, and changes of the heart rate and blood pressure have been recorded following stimulation, ablation, or injury of every part of the brain and cord mentioned above, although some parts, such as the hypothalamus and certain "vital centers" in the medulla oblongata, are more important than others

The peripheral parts of the autonomic nervous system consists of two paravertebral sympathetic ganglionated trunks; various prevertebral and visceral nerve plexuses (such as the cardiac, celiac, and hypogastric, and their branches), the parasympathetic cranial and pelvic splanchnic nerves, and autonomic fibers which are inherent constituents of most of the cerebrospinal nerves.

Visceral activity of a kind can occur through autonomic pathways independent of the brain and cord, but the complex coordination required, for example, for homeostasis, necessitates an overriding direction by higher autonomic and somatic centers operating in integrated harmony *Autonomic reflex arcs* are constructed from afferent, intercalary, and efferent neurons and resemble their somatic counterparts, except that the outgoing pathway is interrupted by a synapse in a peripheral ganglion, so that *preganglionic* and *postganglionic* elements are described, whereas there are no peripheral synapses in the somatic outflow There is no fundamental disparity, however, but merely a difference in the location of the autonomic efferent cells which migrate outwards from the developing neural tube to form peripheral ganglionic masses such as those associated with certain parasympathetic cranial nerves and those of the sympathetic ganglionated trunks and prevertebral plexuses. These are the efferent autonomic cells, and, to maintain structural and functional relationships, the intercalary (preganglionic) axons follow these

and other autonomic ganglia, and the pelvic splanchnic fibers relay mainly in the inferior hypogastric (pelvic) and enteric plexuses. The *postganglionic fibers* associated with the cranial nerves are distributed to vascular and visceral structures in the head, neck, thorax, and abdomen, and *those in the pelvic* splanchnic nerves are distributed to the distal colon and to vascular and visceral structures in the pelvis and perineum

In general, parasympathetic activity produces cardiac slowing and vasodilatation, and these and the opposing sympathetic effects are modified by afferent stimuli received from the heart, vessels, and viscera Many important afferent fibers are conveyed through parasympathetic nerves, such as those in glossopharyngeal filaments from the carotid sinus and body, in the vagus from the heart, aorta, aortic arch bodies, lungs, and abdominal viscera and vessels, and, in the pelvic splanchnic nerves, from vessels and viscera in the pelvis and genitalia

To minimize repetition, additional general details will be given before summarizing *information* about the innervation of the heart and larger arteries

Typically *parasympathetic preganglionic fibers* relay in ganglia situated *near or in the* structure supplied, whereas *sympathetic preganglionic fibers* often relay in ganglia at a distance, so that the parasympathetic postganglionic fibers are relatively short as compared with the sympathetic Also, parasympathetic preganglionic fibers apparently form synapses with a smaller number of efferent cells than the corresponding sympathetic fibers (Wolf, 1941, Samuel, 1953) In consequence of these *anatomic* differences, parasympathetic effects are usually more localized than sympathetic effects, a disparity enhanced by the biochemical and biophysical contrasts in the chemical mediators liberated during sympathetic and parasympathetic activity.

Postganglionic parasympathetic fibers, especially from the *cranial* outflow, follow complicated pathways which need not be detailed here *Postganglionic sympathetic fibers* reach the heart directly in various cardiac nerves, and the aorta and *its* main branches also receive *direct* branches from the nearby sympathetic paravertebral trunks *or their* branches. The postganglionic sympathetic fibers for visceral arteries are carried in branches of the great prevertebral plexuses, and those for the limbs and parietes reach them *indirectly* by running in gray rami communicantes to cerebrospinal nerves, with which they are distributed. They leave these nerves or their branches as they proceed distally and pass in filaments to adjacent vessels at fairly regular intervals. Some nerves, such as the lower trunk of the brachial plexus, the median, the ulnar, the sciatic, the medial popliteal, the phrenic, the intercostals, and the pudendals, contain a relatively high proportion of vascular fibers; and certain arteries receive a disproportionate share of these fibers, such as those in the distal parts of the limbs, those around joints, those with multiple branches, and those supplying the skin and vessels Not all nerves passing to vessels, however, are destined solely for them A *proportion* of the fibers, for example, may have sudomotor and pilomotor functions, and many fascicles alongside visceral arteries carry fibers for the muscular and glandular tissues in these organs The arteries farthest from the heart in the *extremities* have a more profuse innervation than the more proximal vessels because their muscular coats are relatively thicker in proportion to their size and because the vascular nerves *also* carry fibers for the numerous joints, glomera, and skin glands in the hands and feet.

Vascular nerves are slender and seldom more than 4 to 6 cm in length, although some may be longer, e g , filaments accompanying the aorta, and the internal carotid, vertebral, ulnar, external iliac, and deep femoral arteries. The filaments entering the perivascular tissues pursue a slightly sinuous course before branching and forming loops or networks with wide meshes· these should not be confused with the *still finer* terminal nerve networks mentioned below. The fibers in the vascular nerves and plexuses are not entirely efferent (postganglionic). Some of the fibers are afferent, and these are specially numerous in some cardiac and aortic *nerves* and in those supplying the pulmonary trunk, the carotid and femoral bifurcations, etc. Therefore many perivascular *nervelets* do not necessarily imply a rich *efferent supply* On the contrary, they may indicate the existence of special receptor or reflexogenous zones

Branches of *arteries* are innervated by *continuations of the perivascular nerve plexuses*

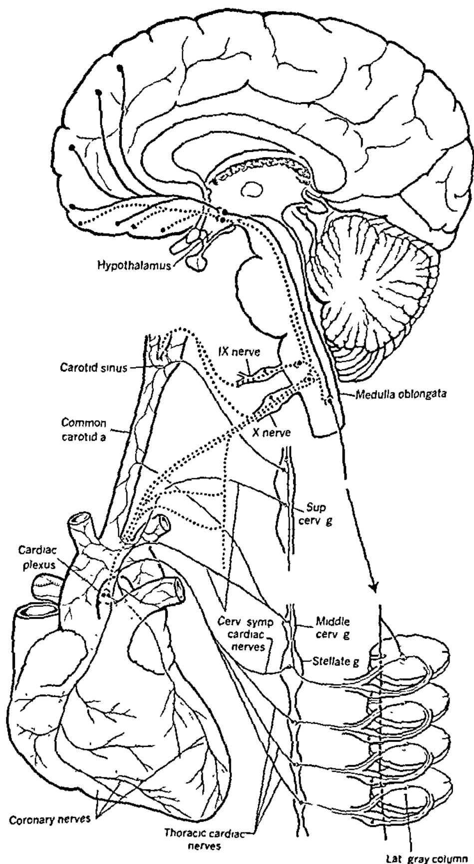


Fig. 1-91. A diagram showing the main nerves (sympathetic—solid lines; parasympathetic—dotted lines) supplying the heart, aortic arch, and carotid sinus, and how "centers" in the medulla oblongata and lateral gray columns of the cord may be influenced by descending pathways from the cerebral cortex and hypothalamus and by afferent impulses carried by fibers in branches of the glossopharyngeal, vagus, and spinal nerves. To avoid overcomplication most of the afferent sympathetic pathways have been omitted.

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Branches of *arteries* are innervated by continuations of the *perivascular nerve plexuses*

around the parent vessel, but some large branches, such as the deep femoral artery and others supplying facial, meningeal, glandular, articular, and pudendal structures, receive increments of fibers from adjacent nerves which augment the filaments continued from the parent vessel. When an artery bifurcates, its accompanying nerves also divide and are continued along the main arterial divisions.

Local fluctuations in blood flow are not produced entirely by variations in the tonicity of the media as a result of vasomotor impulses, with consequent modifications in the lumina of the vessels. Here and there in the arterial tree

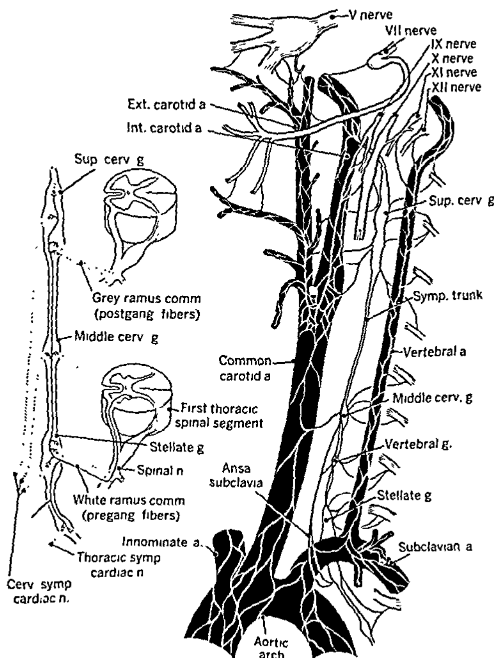


Fig. 1-92. *The larger arteries supplying structures in the head and neck and their main sources of innervation. The inset diagram indicates how preganglionic fibers for these regions pass through the lowest cervical or uppermost thoracic spinal nerves and white rami communicantes to the stellate ganglion. They relay in this ganglion or run upwards or downwards in the sympathetic trunk to form synapses with ganglion cells at higher or lower levels, such as the middle and superior cervical ganglia. The axons of these ganglionic cells join cranial and spinal nerves through gray rami communicantes and are distributed with them to vessels, glands, and other structures supplied by the autonomic nervous system.*

there are *sphincter mechanisms*, as in the arteriolar side of arteriovenous anastomoses, and more mechanical devices such as sessile or pedunculated endothelial cushions (Conti, 1953).

Because of their relatively thick muscular coats, arteries have a richer nerve supply than *veins*, and the supply to smaller veins is sparse and often difficult to detect. Like the arteries, the veins receive filaments from nearby nerves, and microscopic examination of these nerves reveals a considerable proportion of thicker and probably afferent fibers. It has been claimed that the venous adventitia is particularly sensitive to painful stimulation (Pereira, 1946).

Very fine varicose nerve fibers can be seen around many *capillaries*, and many observers are convinced that the ultimate vascular ramifications, as in other structures supplied by the autonomic nervous system, are in the form of a syncytial *terminal nerve network* (or ground plexus) containing small interstitial ganglion cells. Others believe that these networks and cells are connective tissue elements masquerading as nerve fibers and ganglion cells, because of artifacts or misinterpretation (Lazorthes, 1949, Mitchell, 1956).

THE HEART

The heart is supplied by sympathetic and parasympathetic nerves (Fig 1-91) containing both efferent and afferent fibers which are involved in important reflexes

The Sympathetic Cardiac Nerves. The *preganglionic fibers* are the axons of cells located in the lateral gray columns of the cord in the upper fourth to fifth thoracic segments. Leaving the cord in the ventral roots of the corresponding thoracic nerves, they enter white or mixed rami communicantes passing from the spinal nerves to adjacent ganglia in the sympathetic trunks Some relay in these ganglia, and others ascend in the trunks to the cervical ganglia before forming synapses with the ganglionic cells which give origin to the postganglionic fibers these are conveyed to the heart in the sympathetic cardiac nerves arising from the cervical and upper thoracic ganglia

The *superior cervical sympathetic cardiac nerve* arises by one or more rootlets from the superior cervical ganglion and usually unites with the corresponding vagal branch. The conjoint nerve descends behind the carotid sheath and communicates with laryngeal, pharyngeal, carotid, thyroid, and other cervical cardiac nerves The right nerve passes posterolateral to the right subclavian and innominate arteries to the cardiac plexus The left nerve passes between the left common carotid and subclavian arteries or around the root of the latter vessel and curves downwards across the left side of the aortic arch to the cardiac plexus.

The *middle cervical sympathetic cardiac nerve* is often the largest of the sympathetic cardiac nerves and arises from the middle cervical ganglion; it usually receives a contribution from the vertebral ganglion (*ganglion intermédiaire*). On the right side, it enters the thorax behind the subclavian and innominate arteries and reaches the cardiac plexus by passing between the tracheal bifurcation and the aortic arch. The left nerve runs between the left common carotid and subclavian arteries or around the root of the latter, and then crosses the left side of the aortic arch to the cardiac plexus. On both sides, the nerve communicates with thyroid, tracheal, esophageal, and aortic branches, and with filaments from the recurrent laryngeal nerves, especially on the left side.

The *inferior cervical sympathetic cardiac nerve* consists of a variable number of filaments from the stellate ganglion and ansa subclavia. On both sides they run posterolateral to the aortic arch to the cardiac plexus. They often combine or form interconnections with adjacent cardiac and aortic nerves and have inconstant communications with the phrenic nerves

The *thoracic cardiac nerves* were probably first noted by Weber (1815) and were rediscovered by Perman (1924), Kondratjew (1926), and others. They are four to five slender branches from the second to fourth or fifth thoracic ganglia, run directly to the cardiac plexus, and are interconnected with neighboring filaments destined for the trachea, esophagus, aorta and lungs Although minute, they are clinically important, as they contain cardiac accelerator and pain fibers

The Parasympathetic Cardiac Nerves. The parasympathetic fibers are carried in the vagi and the cranial parts of the accessory nerves which join them. The preganglionic fibers originate in the dorsal vagal nucleus, although there is no evidence in primates (Mitchell and Warwick, 1955) of a nucleus cardiacus nervi

around the parent vessel, but some large branches, such as the deep femoral artery and others supplying facial, meningeal, glandular, articular, and pudendal structures, receive increments of fibers from adjacent nerves which augment the filaments continued from the parent vessel. When an artery bifurcates, its accompanying nerves also divide and are continued along the main arterial divisions

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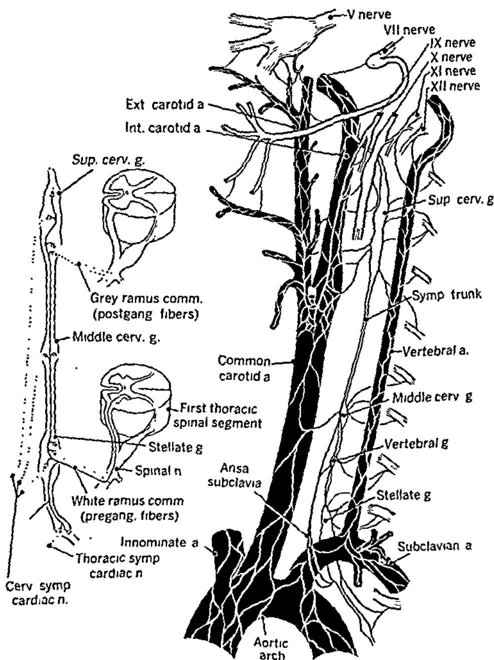


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pulmonary parts of the bronchial arteries are supplied by prolongations from the nerve plexus surrounding the descending thoracic aorta.

The Abdominal Aorta. This aorta has a rich nerve supply, and many of the constituent fibers are continued onwards in and are distributed with the subsidiary plexuses surrounding its branches, a proportion of these fibers are visceral rather than vascular, as in the case of those accompanying the celiac, superior and inferior mesenteric, renal, suprarenal, testicular, and other visceral arteries and their branches

A variable number of twigs reaches the aorta from the lumbar sympathetic trunks, the lumbar splanchnic nerves, and the parailiac nerves (see below). It also receives filaments from the adjacent celiac, superior and inferior mesenteric, and superior hypogastric plexuses. Small ganglia are commonly found in close association with these aortic nerves or with their offshoots along the visceral arteries, as, for example, in the hilus of the kidney

The Common Iliac Arteries. These arteries are supplied by fascicles continued from the lowest part of the abdominal aortic plexus, and these are reinforced on each side by a *parailiac nerve*, which may arise from the second and third lumbar splanchnic nerves, from the intermesenteric nerve plexus, or from the aorticorenal ganglion (Wilde, 1952) The nerve descends alongside the aorta to the common iliac artery and then runs alongside it, giving off filaments which join the *periarterial* plexus Other reinforcing filaments may come from the superior hypogastric plexus (presacral nerve) lying between the diverging arteries, or from adjacent lower lumbar or upper sacral sympathetic trunk ganglia

The Internal Iliac Artery. Branchlets from the common iliac arterial plexus extend on to this vessel, which also gets filaments from the homolateral hypogastric nerve or the upper part of the sacral sympathetic trunk. Direct contributions from the pelvic splanchnic nerves have not been traced to this artery, but its visceral branches, which supply most of the pelvic viscera and genitalia, receive an additional supply through branches of the *inferior hypogastric (pelvic) plexus*, which is a mixture of sympathetic and parasympathetic (pelvic splanchnic) elements As in the case of the other visceral arteries, the paravascular nerves contain both vascular and visceral fibers. Some of the vessels, for example the internal pudendal arteries, are especially well innervated, and their periarterial plexuses receive twigs from the pudendal nerves and their branches

The External Iliac Artery. The periarterial plexus around the commencement of this vessel is continued from the plexus on the common iliac artery, and it is augmented by from two to four strands from the genitofemoral nerve and its genital branch. The highest genitofemoral branch joins the artery near its origin and often unites with a filament derived from the parailiac nerve. The lowest genitofemoral branch joins the artery near the inguinal ligament, and some of its fibers are continued on to the femoral artery Sometimes a long, slender nerve arising from the side of the superior hypogastric plexus may be traced behind the common and external iliac arteries and on to the femoral artery as far as its bifurcation

THE INNERVATION OF THE MAIN ARTERIES OF THE HEAD AND NECK

The Common Carotid Artery. It has a relatively sparse nerve supply (Fig. 1-92), formed mainly by one or two filaments from the middle cervical and vertebral sympathetic trunk ganglia. These may be joined by inconstant contributions from the ansa subclavia and from the cardiac or vagus nerves The upper end of the artery shares in the abundant innervation of the carotid sinus.

The Carotid Sinus. As befits its physiologic importance, the carotid sinus is profusely innervated, and its walls are characterized by rich terminal nerve networks The principal supply is through the carotid branch of the [illegible]

sympathetic fibers are apparently continued through the carotid sinus plexus into the external carotid perivascular plexus. Most of the fibers in the carotid sinus nerves are afferent, although a proportion are efferent (Jabonero, 1951b) Some of the fibers supply the carotid body.

The Internal Carotid Artery. Apart from its lower end, which shares in the carotid sinus innervation, the cervical part of the internal carotid artery (Fig 1-92) has a rather meager supply from fibrils given off by the superior

vagi, as described by Malone (1913–1914). The fibers end by forming synapses in the extrinsic or intrinsic cardiac ganglia, and the postganglionic fibers are relatively short.

The vagal cardiac branches are rather variable, but three groups are generally recognizable.

The *superior vagal cardiac branches* are two to three filaments arising from the vagus below its superior laryngeal branch, and they almost invariably join the superior cervical sympathetic cardiac nerve (see above)

The *middle vagal cardiac branches* consist of one to three nervelets arising from the vagus in the lower half or third of the neck. They always communicate, and sometimes fuse, with the corresponding sympathetic cardiac nerve. On the right side, they descend posterolateral to the innominate artery and aortic arch to the cardiac plexus, and on the left side they lie lateral to the left common carotid artery and aortic arch.

The *inferior vagal cardiac branches* arise at the cervicothoracic inlet or within the superior mediastinum, and they are reinforced, especially on the left side, by fascicles from the recurrent laryngeal nerve. They invariably communicate with other cardiac nerves before entering the cardiac plexus

The Cardiac Plexus. The cardiac nerves mentioned above end in the *cardiac plexus*, which is situated above the base of the heart in the concavity of the aortic arch and between the arch and the tracheal bifurcation It is often artificially and unnecessarily divided into superficial and deep parts, although the preaortic plexus overlying the ascending aorta described by Arnulf (1949) and Hantz (1951) is more superficial, and they advocate its removal for the relief of cardiac pain and to increase the coronary blood flow.

Small ganglia in which parasympathetic and perhaps some sympathetic fibers relay exist in the cardiac plexus. These are the *extrinsic cardiac ganglia*, and the largest is usually located below and to the right of the aortic arch near the attachment of the ligamentum arteriosum.

Filaments from the cardiac plexus supply the adjacent vessels (aorta, pulmonary vessels, and superior vena cava). Other offshoots accompany and form plexuses around the coronary arteries and their branches. Branchlets from the coronary nerves ramify in the subepicardium, and fascicles penetrate and supply the myocardium. Some fibers penetrate to the subendocardium to end in terminal networks or branched endings which are specially evident near the cardiac valves, in the infundibulum, and over the interatrial septum: these are probably special reflexogenous zones.

The FA and AV nodes and the AV bundle are abundantly supplied with nerves associated with minute ganglia. These ganglia belong to the *intrinsic cardiac ganglia*, which are mainly located in the subepicardial tissues over the atria, around the roots of the great vessels, and along the interatrial and AV sulci. It is commonly stated that intrinsic ganglia are not found over the ventricles of mammals (apart from Artiodactyla and Cetacea), but the author (1956) has shown that they do exist in Primates, this finding casts doubts on H H. Woollard's (1926) view that the ventricles are innervated chiefly or entirely from sympathetic sources.

THE INNERVATION OF THE MAIN ARTERIES IN THE THORAX AND ABDOMEN

The Thoracic Aorta. The ascending aorta, aortic arch, and coronary arteries are supplied by offsets from the cardiac plexus, and the descending thoracic aorta receives filaments from the nearby portions of the thoracic sympathetic trunks and thoracic splanchnic nerves These filaments on each side are sometimes interconnected by a delicate vertical strand, the *para-aortic nerve*.

Extensions from the *aortic arch plexus* are continued along and supply the intrathoracic parts of the innominate artery, left common carotid, and left subclavian arteries.

The branches of the descending thoracic aorta (posterior intercostal, subcostal, phrenic, bronchial, esophageal, pericardial, and mediastinal) receive periarterial prolongations from the nerve plexus surrounding the parent vessel

The Pulmonary Vessels. The vessels supplying the lungs and bronchi are innervated through branches from the *anterior and posterior pulmonary plexuses*, which are composed of larger vagal and smaller sympathetic contributions The extrapulmonary parts of the pulmonary arteries and veins, however, receive filaments from the cardiac plexus, and the extra-

pulmonary parts of the bronchial arteries are supplied by prolongations from the nerve plexus surrounding the descending thoracic aorta.

The Abdominal Aorta. This aorta has a rich nerve supply, and many of the constituent fibers are continued onwards in and are distributed with the subsidiary plexuses surrounding its branches, a proportion of these fibers are visceral rather than vascular, as in the case of those accompanying the celiac, superior and inferior mesenteric, renal, suprarenal, testicular, and other visceral arteries and their branches

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THE INNERVATION OF THE MAIN ARTERIES OF THE HEAD AND NECK

The Common Carotid Artery. It has a relatively sparse nerve supply (Fig 1-92), formed mainly by one or two filaments from the middle cervical and vertebral sympathetic trunk ganglia These may be joined by inconstant contributions from the ansa subclavia and from the cardiac or vagus nerves. The upper end of the artery shares in the abundant innervation of the carotid sinus.

The Carotid Sinus. As befits its physiologic importance, the carotid sinus is profusely innervated, and its walls are characterized by rich terminal nerve networks. The principal supply is through the carotid branch of the glossopharyngeal nerve, but it also receives filaments from the vagus and from the superior cervical sympathetic ganglion. Many of the sympathetic fibers are apparently continued through the carotid sinus plexus into the external carotid perivascular plexus. Most of the fibers in the carotid sinus nerves are afferent, although a proportion are efferent (Jabonero, 1951b) Some of the fibers supply the carotid body.

The Internal Carotid Artery. Apart from its lower end, which shares in the carotid sinus innervation, the cervical part of the internal carotid artery (Fig 1-92) has a rather meager supply from fibrils given off by the superior

cervical sympathetic ganglion, and inconstant fascicles from the hypoglossal, vagus, or glossopharyngeal nerves or their branches.

In contrast, the part of the artery within the carotid canal and skull has a plentiful nerve supply, derived mainly from the internal carotid branches of the superior cervical sympathetic ganglion. These branches ramify around the artery and are associated with small ganglia. The internal carotid plexuses of opposite sides become continuous with each other through their continuations along the anterior cerebral and anterior communicating arteries. The other branches of the internal carotid artery (hypophyseal, ophthalmic, middle cerebral, anterior choroidal, and osseous) are also supplied by continuations from the parent periarterial plexus, and these are supplemented by filaments from the trigeminal ganglia or their branches and from the greater superficial petrosal nerves The basal arteries are more richly innervated than the other cerebral arteries and contain a mixture of efferent and afferent fibers

The External Carotid Artery. This artery and its branches have a relatively profuse innervation derived initially from branches from the superior cervical ganglion and the carotid sinus plexus, and reinforced by filaments from adjacent branches of the facial and trigeminal nerves The lavish nerve supply is doubtless associated with the importance of vasomotor phenomena in structures supplied by the artery, although a proportion of the fibers are secretomotor and afferent. for example, the sympathetic supply for the submandibular and sublingual glands is carried in the lingual periarterial plexus, or perhaps more often along the facial and submental arteries, and many of the fibers accompanying the maxillary artery and especially its meningeal branches are probably afferent in function

The Vertebral Artery. Near its origin the vertebral artery (Fig 1-92) is supplied by extensions from the nerve plexus around the parent subclavian artery. It is soon joined by two or more *vertebral nerves*, usually arising from the stellate and vertebral ganglia These ascend with the artery and are usually reinforced by filaments from the middle and superior cervical ganglia Where the artery winds behind the lateral mass of the atlas, the periarterial plexus receives filaments from the first and second cervical nerves and occasionally from the hypoglossal, accessory, or vagus nerves The *basilar plexus* and the subsidiary plexuses around its branches are continuations from the vertebral plexuses. The vessels supplying the parts of the brain and meninges in the posterior cranial fossa also receive vasodilator fibers from the glossopharyngeal and vagus nerves (Stohr, 1921), and afferent fibers from the tentorial branches of the trigeminal nerves.

THE INNERVATION OF THE MAIN ARTERIES IN THE LIMBS

It has been explained that apart from the proximal parts of the large arteries supplying the limbs which receive direct filaments from the sympathetic trunks or their branches, the other vessels in the extremities are supplied by postganglionic vascular fibers which join the spinal nerves through gray rami communicantes (Fig. 1-93). These fibers are conveyed to their destinations in the various branches of the brachial and lumbosacral plexuses, being given off from these nerves in fascicles which pass to adjacent vessels. In the upper limb, the lower trunk of the brachial plexus and the median and ulnar nerves contain most of the autonomic fibers, and this explains the predisposition to vasomotor and trophic disturbances associated with irritation, diseases, or injuries involving these nerve structures The postganglionic vascular fibers for the lower limbs mainly join the roots of the lumbar plexus and the first sacral nerve through gray rami communicantes and are distributed with the femoral, genitofemoral, obturator, sciatic, and popliteal (especially the medial) nerves to adjacent vessels.

The Arteries of the Upper Limb. THE SUBCLAVIAN ARTERY. The plexus around the origin of the right artery is continuous with that of the innominate artery (Fig 1-93), and the intrathoracic part of the left artery is surrounded by an extension from the plexus on the aortic arch (Fig. 1-92) On each side, the proximal part of the artery receives filaments directly from the stellate ganglion and ansa subclavia, and occasionally from the vertebral or middle cervical ganglia or from cervical sympathetic cardiac nerves. This distal part of the artery usually receives additional delicate twigs from the lowest trunk of the brachial plexus.

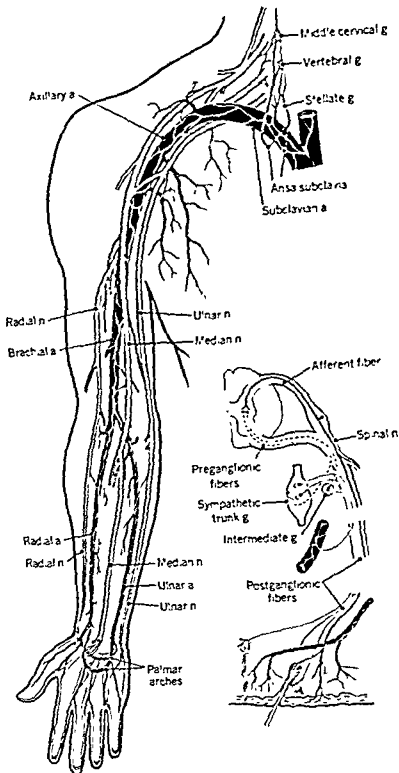


Fig. 1-93 The main vessels of the upper limb and the chief nerves supplying them. The smaller diagram reveals how preganglionic fibers (dotted lines) form synapses with cells in sympathetic trunk or intermediate ganglia and how the axons of these cells (postganglionic fibers—solid lines) rejoin spinal nerves to be distributed to vessels of the cutaneous and of other structures innervated by the autonomic nervous system.

cervical sympathetic ganglion, and inconstant fascicles from the hypoglossal, vagus, or glossopharyngeal nerves or their branches.

In contrast, the part of the artery within the carotid canal and skull has a plentiful nerve supply, derived mainly from the internal carotid branches of the superior cervical sympathetic ganglion. These branches ramify around the artery and are associated with small ganglia. The internal carotid plexuses of opposite sides become continuous with each other through their continuations along the anterior cerebral and anterior communicating arteries The other branches of the internal carotid artery (hypophyseal, ophthalmic, middle cerebral, anterior choroidal, and osseous) are also supplied by continuations from the parent periarterial plexus, and these are supplemented by filaments from the trigeminal ganglia or their branches and from the greater superficial petrosal nerves The basal arteries are more richly innervated than the other cerebral arteries and contain a mixture of efferent and afferent fibers

The External Carotid Artery. This artery and its branches have a relatively profuse innervation derived initially from branches from the superior cervical ganglion and the carotid sinus plexus, and reinforced by filaments from adjacent branches of the facial and trigeminal nerves The lavish nerve supply is doubtless associated with the importance of vasomotor phenomena in structures supplied by the artery, although a proportion of the fibers are secretomotor and afferent for example, the sympathetic supply for the submandibular and sublingual glands is carried in the lingual periarterial plexus, or perhaps more often along the facial and submental arteries, and many of the fibers accompanying the maxillary artery and especially its meningeal branches are probably afferent in function

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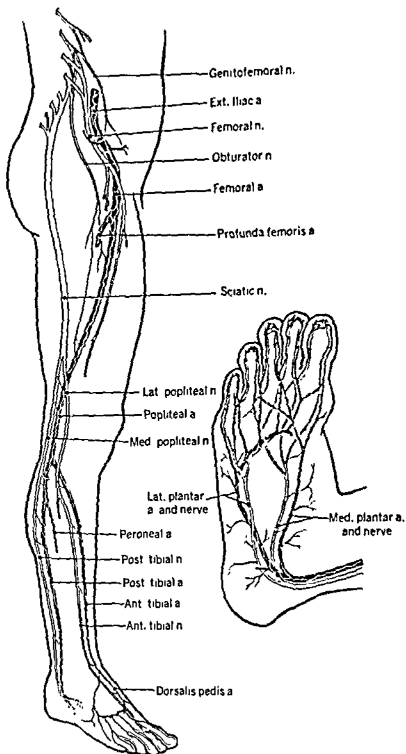


Fig 1-94. The main vessels of the lower limb and the chief nerves supplying them The smaller diagram shows the plantar vessels and their nerve supplies. The routes followed by postganglionic fibers in reaching vessels of the cutaneous and of other structures in the limbs and parietes are illustrated in the previous figure.

Subsidiary plexuses derived from the perivascular plexus around the subclavian artery are continued along its internal mammary, thyrocervical, and costocervical branches, and these subsidiary plexuses may be supplemented by fascicles from nerves lying near these arteries or their branches.

THE AXILLARY ARTERY (Fig 1-93). It is generally believed that the sympathetic fibers derived directly from the sympathetic trunk or its branches extend at least as far as the subclavian-axillary junction. Beyond this level the artery is supplied by sympathetic fibers which have pursued an indirect route through gray rami communicantes to the brachial plexus, and thence through vascular filaments from the plexus or its branches to the artery The perivascular plexus around the upper half of the artery is augmented by filaments from the medial and lateral cords of the brachial plexus, and the distal half of the plexus is joined by one or two strands from the median nerve or its roots of origin

All the arterial branches (superior thoracic, acromiothoracic, lateral thoracic, subscapular, and anterior and posterior humeral circumflex) are innervated by filaments derived from the main axillary periarterial plexus, and as they proceed to their terminations, they also receive twigs from adjacent nerves, e g., the humeral circumflex arteries from the circumflex nerve and the circumflex scapular artery from the subscapular nerves. The plexus on the lateral thoracic artery and its external mammary branch carries many nerve fibers into the mammary gland, where they communicate with those surrounding corresponding branches of the internal mammary and intercostal arteries

THE BRACHIAL ARTERY. This artery (Fig 1-93) carries a prolongation of the axillary arterial plexus, which is reinforced at intervals between the axilla and elbow by from three to four filaments from the median nerve, and by inconstant twigs from the musculocutaneous and radial (musculospiral) nerves The lowest and largest median filament reaches the artery near its termination, it bifurcates with the artery, and the subdivisions follow the radial and ulnar arteries.

The branches of the brachial artery (profunda brachii, nutrient, ulnar collateral, muscular, and supratrochlear) all receive offsets from the plexus around the main vessel. The plexuses are distinct on the arteries forming the anastomoses around the elbow joint, so conforming to the general rule that articular and periarticular vessels are relatively well supplied with nerves.

THE RADIAL AND ULNAR ARTERIES In their proximal parts these arteries are supplied by continuations of the brachial periarterial plexus and by the subdivisions of the lowest median nerve filament reaching the brachial artery. Lower down, the radial periarterial plexus is reinforced by from two to three fascicles from the radial nerve, and the ulnar periarterial plexus is joined by a long slender branch of the ulnar nerve, which can often be traced to the point where the artery gives off its deep branch immediately beyond the pisiform bone

As usual, the arterial branches are innervated by extensions from the plexuses around the main vessels, sometimes supplemented by filaments from adjacent nerves, e.g., the anterior and posterior interosseous arteries get additional filaments from the corresponding interosseous nerves, which are branches of the median and radial nerves, respectively.

THE ARTERIES OF THE HAND The palmar arches are partly innervated by prolongations from the plexuses on the radial and ulnar arteries. The deep arch plexus is joined by one or two twigs from the deep branch of the ulnar nerve and perhaps by radial nerve filaments accompanying the terminal part of the radial artery. The superficial arch receives fascicles from the medial terminal palmar division of the median nerve or its digital branches and from the palmar cutaneous branches of the ulnar nerve. The palmar digital vessels are surrounded by subsidiary plexuses derived from the plexuses around the palmar arches, and these are always reinforced by filaments from the palmar digital nerves.

The dorsal carpal arch and dorsal metacarpal arteries are supplied by subsidiary plexuses derived from the parent radial, ulnar, and interosseous arteries; and the plexuses around the dorsal digital arteries are reinforced by vascular twigs from adjacent branches of the radial and ulnar nerves

The Arteries of the Lower Limb. The buttocks are supplied by many vessels, but the most important are the *superior and inferior gluteal arteries*, which are surrounded by periarterial plexuses continued respectively from

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Vasculature of the neck and head

FRED A. METTLER

ARTERIES OF THE NECK AND EXTERIOR PART OF HEAD

Arteries of Passage. Two main channels of arterial passage to the head lie in the neck. Blood reaches the head directly through (1) the vertebral artery (Fig. 1-95A) and (2) the common carotid (Fig 1-55) by virtue of its continuation as the internal carotid The arch of the subclavian artery, which *carries blood* directly to the upper extremity, also lies in the neck. On the left side, the common carotid and subclavian arteries arise directly from the arch of the aorta (Fig 1-95B) On the right, the brachiocephalic (old term, innominate) artery arises from the aortic arch and then branches into the common carotid and subclavian (*Fig.* 1-95B). The vertebral artery arises from the subclavian (Fig. 1-95A).

ANASTOMOTIC CIRCULATION IN OCCLUSION OF BRACHIOCEPHALIC ARTERY If the brachiocephalic artery is occluded, an elaborate anastomotic circulation develops in order to supply the head and the upper extremity. The anastomotic supply of the head is derived entirely *from the* opposite common carotid and vertebral arteries The structures inside the cranium obtain their blood through the *circle of Willis*, which is adequately supplied from the left internal carotid and *vertebral* arteries. Communications between the two external carotid arteries (Fig 1-96B) serve as the pathway of supply to the deficient right area of the neck The anastomotic arrangement for the right arm is somewhat more complicated Figure 1-95B shows that the internal thoracic (old term, internal mammary) *artery* can convey blood directly from the external iliac, by means of the inferior and superior epigastric channels. The internal thoracic also receives blood from the aorta as a result of flow through the intercostal arteries. The intercostal anastomotic bed communicates, moreover, with the subclavian artery farther laterally than the origin of the internal thoracic. This is because the first and second intercostal arteries arise from the costocervical trunk directly from the subclavian, as shown in Fig. 1-95A. In addition, the intercostal anastomosis can discharge into the axillary artery through the superior thoracic, lateral thoracic, thoracodorsal, circumflex scapular, and subscapular arteries.

Arteries of the Neck Proper. The intrinsic cervical structures, with the exception of those in the anterior triangle of the neck, are supplied by rami of the subclavian artery. The arterial supply to the region of the anterior triangle of the neck is from the external carotid, which also supplies the exterior of the skull (Fig. 1-96).

The Common Carotid Artery. The common carotid artery arises from the brachiocephalic trunk (innominate) on the right side and from the aortic arch on the left (Fig. 1-95B). It enters the neck behind the sternoclavicular joint and the beginning of the innominate vein (Figs. 1-55, 1-56). *In* the lower part of the neck, it lies lateral to the trachea and recurrent nerve, behind the lateral lobe of the thyroid gland and medial to the internal jugular vein and vagus (*Fig. 1-55*). It is at this location that injections for *carotid angiography* are made The inferior thyroid artery passes medially *behind* the common carotid artery, and the middle and inferior thyroid veins pass in front of it. In the carotid triangle, the common

those around the parent vessels, the posterior and anterior divisions of the internal iliac artery. Within the pelvis, they receive additional filaments from the first or second sacral sympathetic ganglia, and in the buttocks from the adjacent gluteal nerves. The *external iliac artery* carries much of the blood supply for the lower limb, its innervation was summarized above.

THE FEMORAL ARTERY (Fig. 1-94). The external iliac plexus is continued on to the femoral artery, but the chief nerve supply of the latter and its branches is provided by twigs derived from the femoral nerve and its muscular, cutaneous, and saphenous branches. A largish twig arising from the posterior division of the femoral nerve passes to the artery close to the origin of its profunda branch, supplying both vessels, and in the subsartorial canal it receives filaments from the saphenous nerve and the nerve to vastus medialis. Many pacinian corpuscles and other sensory endings are present in the adventitia around the region of the arterial bifurcation.

THE POPLITEAL ARTERY. The plexus on the proximal part is continuous with that around the termination of the femoral artery and is reinforced by filaments from the posterior division of the obturator nerve. The remainder of the artery and its branches are supplied by twigs from the medial popliteal nerve and its articular branches: the lateral genicular arteries receive additional fascicles from the lateral popliteal nerve.

THE TIBIAL ARTERIES. The distal part of the popliteal arterial plexus divides and extends on to the proximal parts of both tibial arteries. The posterior tibial artery and its branches get additional filaments from the nerve to popliteus and from the posterior tibial nerve and its muscular branches. The anterior tibial arterial plexus is reinforced by twiglike filaments from the anterior tibial nerve and its muscular branches.

THE ARTERIES OF THE FOOT. The *arteria dorsalis pedis* is supplied by the anterior tibial nerve and its medial terminal division, and the metatarsal and dorsal digital arteries are joined by filaments from the musculocutaneous and sural nerves.

The *plantar arteries* are innervated in their proximal parts by continuations from the rich plexus around the termination of the posterior tibial artery. The more distal parts and the plantar digital arteries receive extra fascicles from the corresponding medial and lateral plantar nerves and their muscular and digital branches.

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Vasculature of the neck and head

FRED A. METTLER

ARTERIES OF THE NECK AND EXTERIOR PART OF HEAD

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subclavian arteries arise directly *from the arch* of the aorta (Fig. 1-95B). On the right, the brachiocephalic (old term, innominate) artery arises from the aortic arch and then branches into the common carotid and subclavian (*Fig* 1-95B) The vertebral artery arises from the subclavian (Fig. 1-95A).

ANASTOMOTIC CIRCULATION IN OCCLUSION OF BRACHIOCEPHALIC ARTERY. If the brachiocephalic artery is occluded, an elaborate anastomotic circulation develops *in* order to supply the head and the upper extremity. The anastomotic supply of the head is derived entirely from the opposite common carotid and vertebral arteries The structures inside *the cranium* obtain their blood through the *circle of Willis*, which is adequately supplied from the left internal carotid and vertebral arteries Communications between the two external carotid arteries (Fig 1-98B) serve as the pathway of supply to the deficient right area of the neck. The anastomotic arrangement for the right arm is somewhat *more complicated*. Figure 1-95B shows that the internal thoracic (old term, internal mammary) artery can convey blood directly from the external iliac, by means of the inferior and superior epigastric channels. The internal thoracic also receives blood from the aorta as a result of flow through the intercostal arteries The intercostal anastomotic bed communicates, moreover, with the subclavian artery farther laterally than the origin of the internal thoracic. This is because the first and second intercostal arteries arise from the costocervical trunk directly from the subclavian, as *shown in* Fig. 1-95A. In addition, the intercostal anastomosis can discharge into the axillary artery through the superior thoracic, lateral thoracic, thoracodorsal, circumflex scapular, and subscapular arteries.

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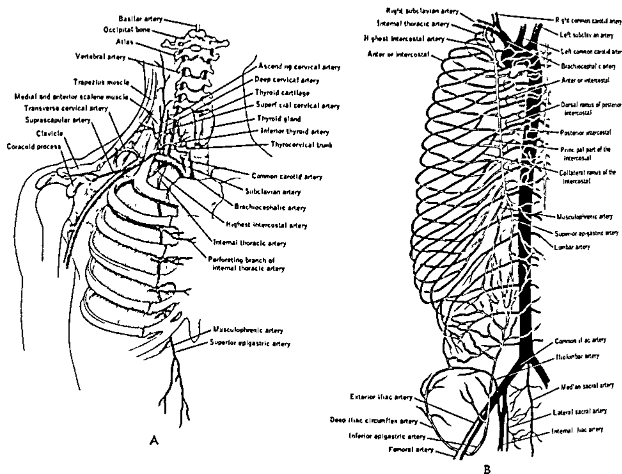


Fig. 1-95. A. Branches of the subclavian arteries B. Origin of the brachiocephalic, common carotid, and subclavian arteries. (*From Mettler. The Medical Sourcebook. Boston, Little, Brown, 1950, after Henle*)

carotid is farther in front, but still medial, to the internal jugular vein and vagus nerves. Ordinarily it divides into the internal and external carotid arteries somewhere below the great horn of the hyoid bone, but variations in the level of the bifurcation have been studied for over two centuries (Henle) Adachi (1928) gave the frequency with which the common carotid branched at the various cervical vertebrae, in Japanese, as follows CII, 1 per cent, CIII, 16 per cent, CIV, 66 per cent, CV, 16 per cent. The common carotid gives off no branches in the neck except to the carotid body

ANASTOMOTIC CIRCULATION IN OCCLUSION OF THE COMMON CAROTID ARTERY If one common carotid artery is occluded, the defective intracranial supply to the circle of Willis is augmented by an increase in flow from the remaining three intracranial sources of supply In addition, blood flows into the deficient carotid reservoir from anastomoses with the subclavian reservoir of the same side and the external carotid reservoir of the opposite side. The former connection is established (1) between the inferior thyroid artery, which comes from the subclavian and the superior thyroid (a branch of the external carotid) and (2) by connections between the deep and ascending cervical arteries (branches of the subclavian) (Fig 1-95A) and the sternocleidomastoid branch of the occipital artery (a branch of the external carotid) (Fig 1-96A). Excellent graphic representations of the collateral connections of the carotid system appear in the book by Lanz and Wachsmuth

Carotid Body The carotid body, or *glomus*, is a reddish-brown, solid object on the deep side of the bifurcation of the common carotid Like the aortic body, it contains chemoreceptors, which respond primarily to anoxia but also to hypercapnia and acidosis Stimulation of the carotid body results in hyperpnea, tachycardia, increased cardiac output, and a drop in peripheral resistance, the last three of which are dependent upon stretch receptor reflexes

from afferents in the lung. *If respiration* is controlled or the afferents from the lung are severed, the reverse effects are encountered.

The afferent fibers from the chemoreceptors are small (2 to 5 μ), myelinated fibers which lie within the carotid sheath and compose a part of the nerve plexus on the *arteries*. They are derived from cells in the sensory ganglia of the glossopharyngeal and vagal nerves and from the *superior cervical ganglion*. Some from the latter reach *it directly, others* arrive via the *internal carotid* plexus. The glomus is about 7 mm long, 4 mm wide, and 2 mm thick, but it may be *represented* by several smaller *continuous masses*. An arterial branch from the *common carotid* enters its caudal pole and drains into venous channels which empty into the facial vein.

Carotid Sinus. Beginning at about the fourth year of age, a certain degree of dilatation can be perceived *in one of the* carotids near the bifurcation of the common carotid. This becomes more marked as the individual matures. Usually it is the internal carotid, occasionally the common carotid, which develops a definite sinus. Only rarely is the carotid *sinus developed* in the external carotid. Usually the left carotid sinus is more pronounced than the right. Within the adventitia of the wall of the carotid sinus (and also in scattered positions elsewhere in the common carotid artery, as well as at the origin of the right subclavian artery) are found *pressoreceptors*. Like those in the aortic arch, these pressure-sensitive elements give rise to impulses which cause bradycardia. The specific stimulus that activates them is deformation of *the wall of the* vessel, rather than a *rise in intraluminal* pressure. The cells of *origin of the fibers related to the* sinus pressoreceptors lie in the glossopharyngeal *ganglia which* give rise to the sinus nerve.[1]

Internal Carotid Artery. The internal carotid artery is the posterior of the two branches of the common *carotid* (Figs. 1-55, 1-56). It lies just *in front* of the transverse *processes* of the cervical vertebrae and deep (*medial*) to the styloid process of the temporal bone and stylohyoid ligament. According *to* Boldrey et al, the transverse process of the atlas [illegible] [illegible]

[illegible] that head [illegible] tends to *occlude* flow only *through* the ipsilateral internal carotid, i.e., the one on the side toward which the head is turned. It would seem instead that the atlas, styloid process, and stylohyoid ligament would compress the vessel on the opposite side and the axis would compress the *ipsilateral* vessel.

At its origin, the internal carotid is the frequent site of prominent *atherosclerotic plaques*, which play an important *role in reduction* of blood flow through the middle cerebral artery and, as a result of thrombosis of the vessel *in* the neck, in the development of cardiovascular accidents.

At its origin, the internal carotid is close *to* the internal jugular vein and presents, *initially*, a slight lateral curve, which brings *it lateral to* the *external carotid*, from which it can be distinguished by the fact that it gives off no branches *in* the neck. It soon curves *medially* toward the posterior belly of the digastric and *extends* upward *to the* carotid canal in the petrous part *of the temporal* bone.

ANASTOMOTIC CIRCULATION IN OCCLUSION OF THE INTERNAL CAROTID. Since the internal carotid has no branches in the neck, blood must reach its cranial distribution either through the *circle* of Willis or through connections [illegible] the ophthal-[illegible]

[illegible] external carotid artery (Fig. 1-96) passes upward *in front* of the internal carotid, medial to the *digastric* muscle. Above this muscle, *it* curves backward *and upward* in the thyroid region. It gives off six branches. (1) At its origin it gives off the *superior thyroid artery*, which arches downward beneath the infrahyoid muscles to supply the lateral lobe of the thyroid gland, and gives off infrahyoid and sternocleidomastoid branches and the *superior* (old term, internal) laryngeal artery. (2) *The lingual artery arises just behind* the great horn of the *hyoid bone*, arches upward over the horn, *and* extends forward medial *to the* hypoglossal nerve and hyoglossal *muscle and* supplies the tongue. (3) The *facial* (old term, external maxillary) *artery* (Fig. 1-96) arises medial to the *posterior belly of the* digastric. (4) The *occipital artery* arises *from* the external carotid and passes backward beneath the *posterior* belly of the digastric and the sternomastoid to the occipital region. The posterior meningeal artery originates from it. (5) *The ascending pharyngeal artery*, a slender *branch* from the medial sur-

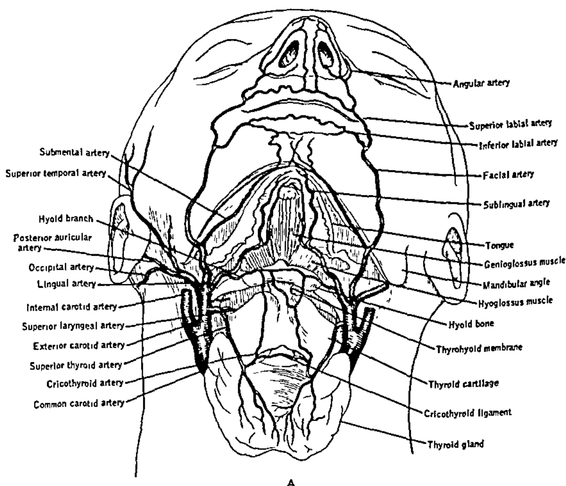
[1] See also Part 2, Chap. 12. *Editor.*

face of the external carotid, supplies the pharynx. (6) The *posterior auricular artery* arises from the posterior part of the external carotid and extends upward through the parotid gland. Behind the mandibular joint, the external carotid artery terminates by dividing into the superficial temporal and the maxillary (old term, internal maxillary) artery. These two vessels are of interest since the former vessel *is the site of temporal arteritis and the latter* gives rise to the important *middle meningeal artery*, which occasionally gives rise to the variably present accessory meningeal artery.

Subclavian Artery. It is customary to divide the subclavian artery (Fig. 1-56) into three parts. (1) the ascending part, from its origin to the medial border of the anterior scalene muscle, (2) the costal part, which is deep to *this muscle (sometimes the artery actually* penetrates the muscle); and (3) the descending part, which lies between the lateral border of the anterior scalene and the lower edge of the first rib, at which point the subclavian becomes, by definition, the axillary artery. On the right, *only the first two parts* of the subclavian and the medial half of the third part lie in the root of the neck. On the left side, the beginning of the first part also lies outside the neck. With the exception of the *internal thoracic* (old term, internal mammary) and *highest intercostal artery* (when this arises directly from the subclavian), all branches of the subclavian artery supply structures in the neck (Figs. 1-56, 1-95A).

The branches of the ascending part of the subclavian artery are the vertebral, the internal thoracic, and the thyrocervical trunk.

VERTEBRAL ARTERY. The vertebral artery continues into the skull to unite with its fellow of the opposite side to become *the basilar artery*, which then splits to become the posterior cerebral. The vertebral is the first and largest branch of the subclavian. *It arises very deeply* behind the internal carotid and in front of the medial edge of the anterior scalene muscle, the transverse process of the seventh cervical vertebra, and the inferior cervical ganglion The latter sends branches to form a plexus around



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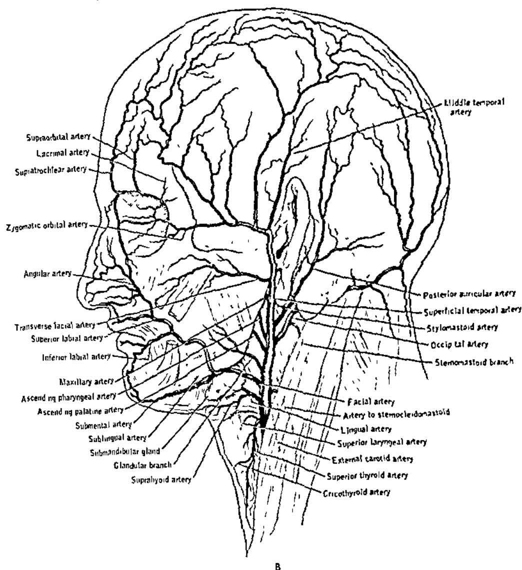


Fig 1-96 External carotid artery and its branches A, from the side of the head, B, from the front of the neck (*From Mettler, The Medical Sourcebook. Boston, Little, Brown, 1959; after Henle.*)

it On its medial side is the sympathetic trunk At the level of the sixth cervical vertebra, it enters the foramen in the transverse process (against the prominent anterior or "carotid" tubercle of which the common carotid is compressible) of this bone and continues upward through the foramen transversarium of each of the upper six cervical vertebrae. Injections for vertebral angiography are made by directing the needle to that part of the artery which passes between the transverse processes of the fifth and sixth cervical vertebrae. Flow through the vertebral artery may be compromised in the spaces between the vertebrae by *osteophytes* developing on the edges of the vertebrae Since rotation of the head is accomplished by movement between the first and second cervical vertebrae, there is a tendency for occlusion of the vertebral artery to develop where it passes through the first transverse process. Toole and Tucker found that turning the head to either side was likely to reduce flow in both vertebral arteries rather than selectively on one side or the other. Compression of the vertebral artery by the anterior scalene muscle has been blamed for episodic vertigo

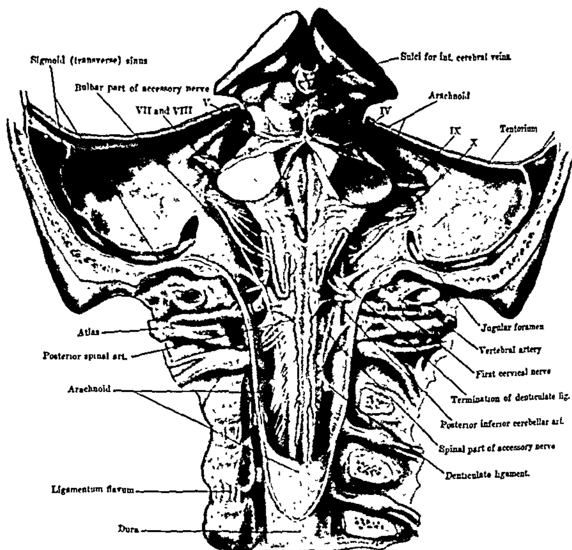


Fig. 1-97. Entrance of the vertebral artery into the subarachnoid space. The origin of the posterior inferior cerebellar arteries may be more rostral than shown here. Sometimes the posterior inferior cerebellar arteries form a congeries in the cisterna magna, causing a risk of cisternal puncture, but ordinarily the appearance of the posterior inferior cerebellar artery below the level of the foramen magnum means displacement due to increased intracranial pressure. (*From Mettler. Neuroanatomy. St. Louis, Mosby, 1948.*)

and tinnitus, but it is difficult to see how such compression would occur or why the described symptoms should result

Between the first cervical vertebra and the skull the vertebral artery bends backward in the vertebral arterial sulcus, which is a groove on the dorsal arch of the atlas The vessel then pierces the posterior atlanto-occipital membrane and dura (Fig 1-97). In its course above the atlas, the first cervical nerve lies ventral to the vertebral artery and the occipital vein lies between it and the base of the skull Having pierced the dura, the vertebral artery passes upward and forward about the lateral side of the spinal cord between the roots of the hypoglossal nerve ventrally and the upper part of the denticulate ligament dorsally It then enters the foramen magnum. Its farther course is described later.

Occasionally the vertebral arteries pass through the *foramen transversarium* of the fifth or seventh cervical vertebra, but ordinarily the foramen of the seventh cervical vertebra is occupied only by vertebral veins The vertebral artery of the left side occupies such a position more frequently than does that of the right. The vertebral arteries are sometimes represented only by a markedly attenuated vessel. Abnormal development of the transverse process of the seventh cervical vertebra constitutes a *cervical rib* In its course between successive transverse processes, the vertebral artery usu-

ally gives off *spinal rami*, which pass along the spinal roots of the second to sixth cervical nerves and supply the corresponding segments of the spinal cord. Since the cord segments are shorter than their corresponding vertebrae, the spinal rami are forced to ascend within the neural canal for a variable distance. The spinal rami of the vertebral arteries are quite variable. Usually one or two are prominent on each side and the others are difficult to locate.

At the entrance of the vertebral artery into the atlanto-occipital membrane, one or more meningeal rami are distributed to the dura of the region, including that of the posterior cranial fossa. These meningeal filaments anastomose with the meningeal rami of the occipital, ascending pharyngeal, and middle meningeal arteries Some of the meningeal filaments of the vertebral also supply the bone in the region of supply.

THYROCERVICAL TRUNK. This branch gives off a highly variable arrangement of branches (1) Very frequently a prominent inferior thyroid artery passes toward the lower part of the thyroid, giving off an ascending cervical artery in its course (Fig 1-95A). The inferior thyroid itself runs to the lower part of the thyroid gland and larynx and to the upper part of the trachea The ascending cervical artery ascends on the surface of the transverse processes between the anterior scalene and longus capitis muscles and gives branches to them. It also contributes spinal rami which supplement those from the vertebral artery. (2) A suprascapular (old term, transverse scapular) artery is also regularly found (3) A variable third common branch, the transverse cervical artery, divides into an ascending branch (the superficial cervical artery), and a deep (old term, descending) branch [the descending (old term, posterior) scapular artery]. The latter may arise from the subclavian artery instead of from the thyrocervical trunk Not infrequently the superficial cervical artery arises independently of the thyrocervical trunk

INTERNAL THORACIC ARTERY (Fig 1-95). It arises from the subclavian and, passing deep to the clavicle, continues deep to the costal cartilages just to the side of the lateral margin of the sternum. It gives off the anterior intercostal branches and, becoming the superior epigastric artery, communicates, through this, with the inferior epigastric

COSTOCERVICAL TRUNK On the right, the second part of the subclavian artery usually gives rise to the costocervical trunk, which lies behind the anterior scalene on that side. On the left, it lies medial to the muscle. The costocervical trunk ordinarily gives rise to the deep cervical and highest intercostal arteries but these may arise independently and from the subclavian artery itself. These vessels are of particular interest in that they send branches to the seventh and eighth cervical nerves and first and second thoracic. In its upward course, the deep cervical artery anastomoses with the vertebral artery and, in the first and second intercostal spaces (especially the latter), the highest intercostal artery anastomoses with the posterior intercostal rami of the aorta. Thus, the upper six cervical segments of the spinal cord receive their arterial blood primarily from the vertebral artery and the lowest 10 thoracic, and all the lumbosacral, segments receive their arterial blood from the aorta Between these two large reservoirs the gap in the arterial supply is provided for by branches of the costocervical trunk. The author (1948) has mentioned that circulatory dysfunctions frequently develop in the area where the blood supply is shifted from the subclavian reservoir (second thoracic vertebra and above) to the aortic reservoir (third thoracic and below). Such an area is presumably subject to relative vascular failure because of the operation of Poiseuille's law Zulch (1954) has described softening in this region as the apparent result of a reduction in blood pressure

ARTERIES OF THE BRAIN AND SPINAL CORD

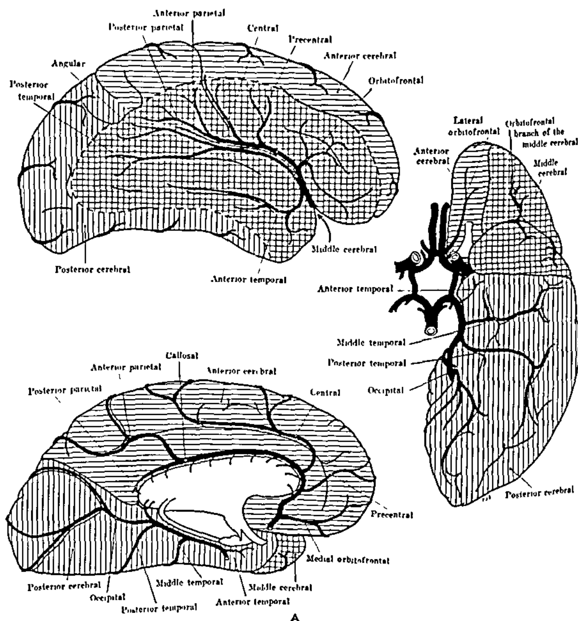
The blood supply of the brain (Fig. 1-98) is derived from two main sources· (1) the vertebral arteries, which supply the back of the cerebrum and the infratentorial portions, and (2) the internal carotid artery, which supplies the front of the cerebrum.

Vertebral Artery. Two vertebral arteries (usually of unequal size) enter the *foramen magnum*, one from each side of the ventrolateral aspect of the upper cervical cord. Occasionally, only one vertebral artery is of significant magnitude. The two vertebral arteries unite on the ventral surface of the medulla, just below the posterior border of the pons (Fig 1-99). Before uniting, each gives off (Fig 1-97) a posterior inferior cerebellar artery (Adamkiewicz's vertebrocerebellar artery)

and spinal branches to the posterior and anterior surfaces of the spinal cord. The posterior branches continue independently down the posterolateral sulcus of the spinal cord and are then called posterior spinal arteries, but the anterior spinal branches promptly fuse to form the unpaired anterior spinal artery which occupies the anterior sulcus of the spinal cord.

The posterior inferior cerebellar artery passes dorsolaterally around the medulla oblongata. Usually it passes between the superficial origins of the vagus and the internal, cranial, or accessory part of the eleventh nerve (Fig. 1-100), but it may be found in many other situations (Figs. 1-97, 1-99). It supplies the posterior or undersurface of the cerebellum (see also page 1-239(Supp.).

BASILAR ARTERY. The basilar artery is formed by the direct union of the two vertebrals. If only one vertebral artery is present, the basilar is the continuation of it. The vertebrals may fuse imperfectly, so that the basilar may be double or even triple in part of its course. It lies on the ventral surface of the pons in a median depression called the *basilar sulcus*, and it gives off two pairs of important branches The *anterior inferior cerebellar artery* arises near the posterior border of the pons It passes backward and is distributed to the portion of the undersurface of the cerebellum nearest the pons It anastomoses with the posterior inferior cerebellar artery. The *superior cerebellar artery*, which arises near the anterior border of the pons, is often double. It winds dorsally



A

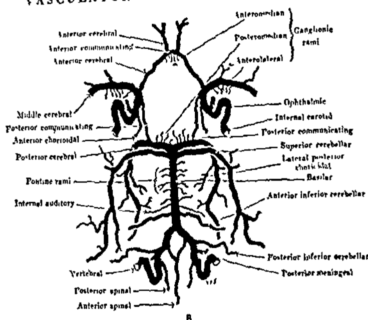


Fig 1-98 A Approximate areas of brain supplied by the three principal cerebral arteries. (The official anatomic terminology for the cortical branches of these arteries is not very useful for arteriography; a more descriptive system is presented above.) (*From Mettler, Neuroanatomy.* St Louis, Mosby, 1948)

Anterior cerebral artery. The orbitofrontal branches of the anterior cerebral are sometimes called prefrontal. The precentral branch is also known as the frontopolar, and one or more central branches are sometimes called internal frontal or, if single, the callosomarginal. The continuation of the anterior cerebral on the callosum may be known as pericallosal instead of callosal, and the anterior parietal as the paracentral with precuneal and parieto-occipital branches.

Middle cerebral artery. Near the base of the lateral cerebral fissure, the middle cerebral artery lies upon the surface of the insula. It here gives rise to the frontoparietal branch, which then gives rise to orbitofrontal, precentral or prerolandic, central or rolandic, anterior and posterior parietal branches It is sometimes called the ascending frontal artery or "candelabra." After giving rise to the anterior temporal branch, the middle cerebral then continues in the lateral fissure, sends off posterior temporal rami, and terminates as the angular (terminal or occipitoparietal artery).

Posterior cerebral artery The branches of the occipital ramus of the posterior cerebral artery are the parieto-occipital (the dorsally located one) and calcarine (that to the calcarine fissure).

In about 10 per cent of cases the posterior and middle cerebral arteries both supply the occipital pole

B. Diagram of the arterial circle.

along the anterior edge of the pons and is distributed to the upper surface of the cerebellum. Sometimes it penetrates the sensory part of the fifth cranial nerve, and sometimes the basilar artery itself passes through a hole in the sella. The anterior and posterior inferior cerebellar arteries sometimes arise from a common stem, which may itself arise from either the basilar or vertebral arteries Between the anterior inferior and the superior cerebellar arteries, a large number of small arteries are given off These are the rami to the pons (or *transverse arteries*). A small branch that travels over the eighth cranial nerve, the labyrinthine (old term, internal auditory) artery, is also given off from the basilar in less than 50 per cent of cases. More commonly it arises from the posterior inferior cerebellar artery. It gives branches to the seventh and eighth nerves, as well as to the labyrinth.

Considerable variability in the size and origins of the inferior cerebellar and labyrinthine arteries occurs. It is not at all uncommon for the anterior inferior cerebellar artery to go

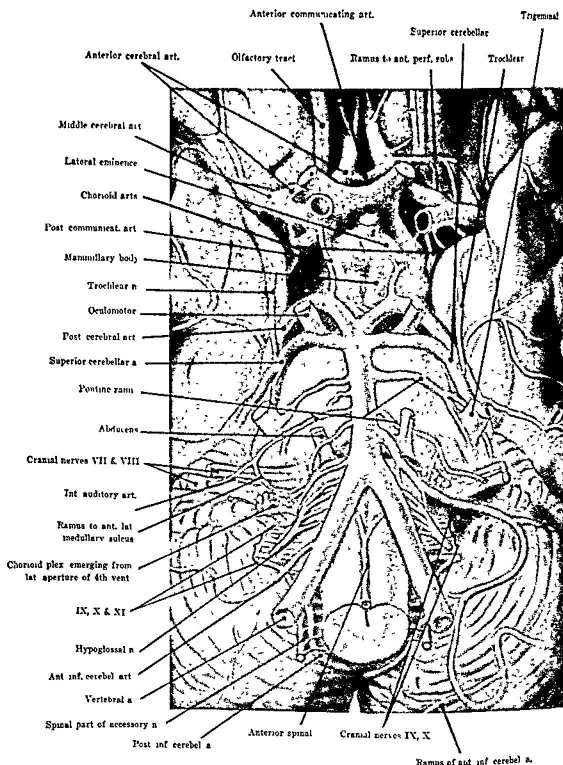


Fig. 1-99. Arteries of the base of the brain, as seen from below (cf Fig 1-100). The anterior poles of the frontal lobes have been separated by a wooden block to show the extension of the anterior cerebral artery into the great longitudinal fissure On the reader's right the posterior communicating artery has been cut off to show the vasculature of the hypothalamic region (cf. Fig. 1-105B). On the right side of the brain (left of illustration) no definite anterior inferior cerebellar artery was present, its place having been taken by a number of smaller vessels coming off independently of one another, each being derived from the main sources of supply (the basilar and right vertebral, in this case) Such variations may occur in many regions of cerebral blood supply The exact point of origin of the posterior inferior cerebellar arteries is particularly subject to variation The situation seen on the reader's right is that which is usually "normal." *(From Mettler. Neuroanatomy. St. Louis, Mosby, 1948)*

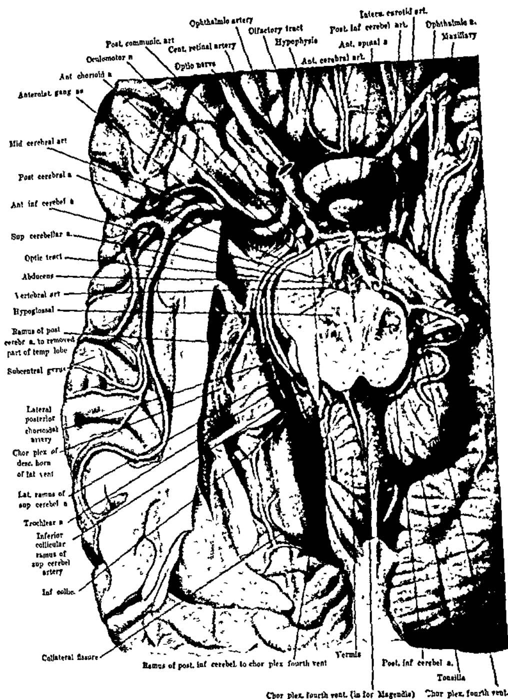


Fig 1-100 Course and branches of the middle and posterior cerebral arteries, and of the choroidal rami to the choroid plexus of the descending horn of the lateral ventricle. Part of the base of the brain is seen from below, the inferior horn of the lateral ventricle having been opened The anterolateral ganglionic rami of the middle cerebral artery are well shown These are longest laterally and medially (lateral lenticulostriate and lenticulo-optic groups, respectively). (See Fig 1-105A) Notice that the posterior inferior cerebellar artery supplies the lateral and dorsal aspects of the medulla The anterior inferior cerebellar artery provides blood to the caudal border of the pons (and also to the rostral end of the restiform body), while the superior cerebellar artery (Fig 1-104) supplies the brachium conjunctivum, anterior medullary velum and tectum (through the medial ramus), and anterior lobe of the cerebellum (through the lateral ramus). Usually the choroid plexus of the fourth ventricle receives most of its blood supply from the main part of the posterior inferior cerebellar arteries, but small, supplementary offshoots from the anterior inferior cerebellar and even internal auditory arteries are not rare (*From Mettler. Neuroanatomy St. Louis, Mosby, 1948*)

deeply into the fissures and sulci of the cerebellum and present very few superficial branches.

POSTERIOR CEREBRAL ARTERY. Shortly after giving off the superior cerebellar arteries, the basilar artery divides into the two posterior cerebral arteries, which pass backward between the upper surface of the cerebellum and the undersurface of the hemispheres, to be distributed to the posterior part of the brain, as will be considered later. The *oculomotor nerve* lies between the origin of the posterior cerebral

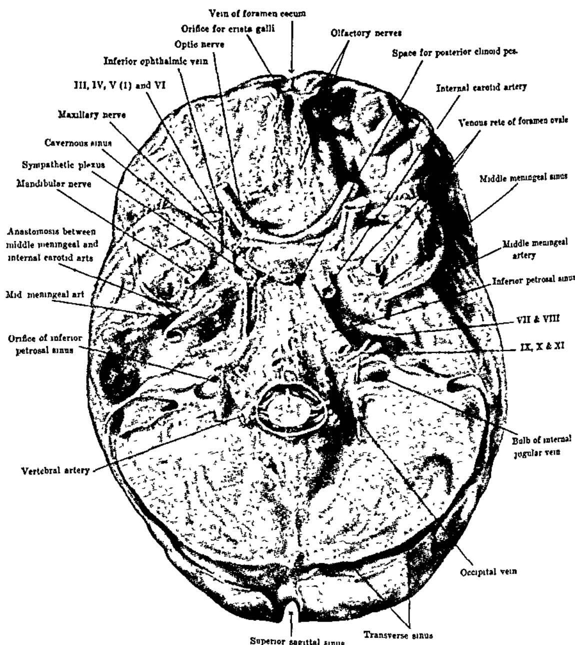


Fig. 1-101. Dura of the base of the brain, seen from below On the right side of the brain (reader's left) the inferior petrosal sinus and cavernous sinus have been opened to display the contained cavernous portion of the internal carotid artery The petrous portion of the internal carotid, which normally occupies an intraosseous position in the carotid canal, is attached to the cavernous sinus On the reader's right, the intraosseous portion of the internal carotid has been removed and the junction of the inferior petrosal sinus with the jugular bulb has been severed. This allows the sheath of the ninth, tenth, and eleventh cranial nerves to fall laterally and forward A number of straws are seen. One passes from the jugular bulb through the occipital vein Two pass from the cavernous sinus, one through the inferior ophthalmic vein and the other through the venous rete of the foramen ovale. (*From Mettler. Neuroanatomy St. Louis, Mosby, 1948.*)

and superior cerebellar arteries The posterior cerebral artery develops embryologically from the internal carotid, but between the fourth and fifth weeks of development, it is shifted over to the vertebral reservoir. Occasionally its origin from the internal carotid persists.

Internal Carotid Artery. PETROUS AND CAVERNOUS PORTIONS. The internal carotid artery reaches the base of the brain by passing through the floor of the skull This is the *petrous portion* of the internal carotid Its *cavernous portion* lies in the groove for the carotid. It emerges from this just lateral to the optic chiasm (Fig 1-101). In the petrous portion of the temporal bone, it gives rise to the caroticotympanic artery and the artery of the pterygoid canal In the cavernous sinus, it gives off branches to the walls of the cavernous and inferior petrosal sinuses, branches to the hypophysis and semilunar ganglion, and the anterior meningeal and ophthalmic arteries. Sometimes the anterior meningeal artery is tardy in its origin and arises from one of the branches of the ophthalmic instead of directly from the carotid.

BRANCHES OF CEREBRAL PORTION. After giving off the ophthalmic artery, the internal carotid lies close to the base of the brain, and the remaining (or cerebral) portion gives rise (Fig 1-98) to (1) a *posterior communicating artery* (absent in about 5 per cent of cases), which runs caudally and anastomoses with the posterior cerebral artery, and (2) an *anterior choroid artery* (inferior choroidal, Sterzi's artery of the archipallium), which swings laterally into the substance of the brain between the cerebral peduncle and the temporal lobe (Figs. 1-99, 1-100). Occasionally, the posterior cerebral is a continuation of the posterior communicating, and is thus a branch of the internal carotid rather than of the basilar artery The anterior choroid artery frequently arises from the middle cerebral artery (see Fig 1-100). The next branch of the internal carotid is (3) the *anterior cerebral artery*, which may be absent on one side It passes first medially and then dorsally above the optic nerve, and is continued as the artery of the corpus callosum (see Fig 1-98).

The internal carotid is considered to terminate where the anterior cerebral is given off. Its continuation into the lateral cerebral fissure is (4) the *middle cerebral artery* (artery of the Sylvian fossa).

Cerebral Arterial Circle. Just in front of the optic chiasm, the anterior cerebral artery unites with its fellow of the opposite side by means of the anterior communicating artery, which may be double or absent. If the anterior communicating artery is absent, the two anterior cerebrals *form a common* trunk for some distance.

Examination thus reveals a complete anastomotic arterial circle about the hypophyseal stalk at the base of the brain (Figs. 1-98, 1-105). This is called the *cerebral arterial circle (of Willis)* and is composed of (1) the proximal parts of the two *posterior cerebral arteries* and their union in the basilar, (2) the two *posterior communicating arteries*, (3) the two internal carotids, (4) the proximal part of the two anterior cerebrals, and (5) the anterior communicating artery Portions of the circle of Willis (the caudal and oral parts) give off fine branches which immediately pass deeply into the brain. These are the anteromedial and posteromedial ganglionic branches, which are of the class called terminal or end arteries, i.e., arteries that form no adequate terminal anastomoses. The anteromedial ganglionic rami arise from the anterior cerebral artery, and the posteromedial ganglionic rami are direct branches of the posterior cerebral arteries and also branches of anastomotic channels in the interpeduncular fossa—the interpeduncular plexus.

The anterolateral ganglionic arteries (Figs. 1-98, 1-100) compose a perforating arterial group which arises from the middle cerebral artery Three groups of vessels make up the anterolateral ganglionic arteries (Fig 1-105). These are (1 and 2) a lateral and medial lenticulostriate group (also called external and internal striate branches), and (3) a lenticulo-optic group which may be represented by a single vessel of variable origin. Quite commonly the lenticulo-optic arteries are grouped with the internal striate rami. As indicated above, the anterior choroid artery frequently arises from the middle cerebral.

Arterial Supply of the Cerebral Cortex. The cerebral cortex is supplied by blood through cortical branches of the anterior, middle, and posterior cerebral arteries The exact terminology of the cortical branches of these three primary vessels is in an unsatisfactory state. They are officially called *rami corticales*, and then are designated as orbital, frontal, temporal, parietal, parieto-occipital, or occipital, ac-

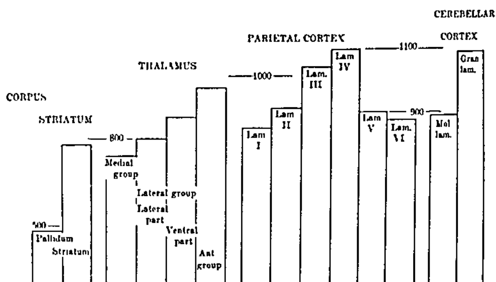


Fig. 1-102. Relative vascularity of various portions of the brain (feline), expressed in terms of millimeters of capillary per cubic millimeter of neural tissue. The underlying white matter receives about 200 mm of capillaries per cubic millimeter. (*Based on data obtained by A. C. P. Campbell*) (*From Mettler Neuroanatomy. St Louis, Mosby, 1948.*)

cording to their general location This terminology does not help to differentiate these vessels precisely, with regard, for example, to a central location as contrasted with a precentral one, and many authors have attempted to designate individual vessels more exactly. Such a scheme is shown in Fig 1-98

The cortical arteries break up into a network in the pia as this lies on the surface of the cortex. From this pial net, delicate "short" vessels run down to the fourth cortical lamina The fourth and lower layers of cortex are also supplied by stouter "long" vessels which do not contribute branches to the upper cortical layers. In this way, the fourth cortical lamina has a dual supply and has a much richer capillarity (Fig 1-102) than do the layers above or below it The long branches of the cortical pial net penetrate into the white matter There is often a certain amount of overlapping of medullary areas supplied by neighboring arteries. The supply to the deeper parts of the white matter is overlapped by the various perforating vessels of the base of the brain Very few cortical arteries send any branches into the territory of the internal capsule itself (Fig. 1-103).

Arterial Supply of Deep Substance of the Brain. The deep substance of the brain is supplied by arterial blood through the ganglionic vessels, which perforate the substance of the base (as noted above) or enter the choroidal fissure (Fig. 1-100). The *Nomina Anatomica Parisiensia* (*PAN*) refers to these casually as central branches of the anterior, middle, and posterior cerebral artery, a choroidal artery, and a choroidal ramus of the posterior cerebral artery

Alexander (1942) uses the term "striate branches" for what the *PAN* calls perforating rami of the anterior, middle, and posterior cerebral arteries

ANTERIOR CHOROIDAL ARTERY. Carpenter, Noback, and Moss (1954) found that the choroid artery, more appropriately designated by an older name as the anterior choroid, originated from the internal carotid in 76.6 per cent of cases, from the middle cerebral artery in 11.7 per cent, from the posterior communicating in 6.7 per cent, and from the junction of the anterior and the middle cerebral arteries in 3.3 per cent of cases. It is sometimes absent

POSTERIOR CHOROIDAL ARTERY. The vessel known in the *PAN* as the choroid ramus of the posterior cerebral artery has long been called the posterior choroid artery It has been designated by Mettler as the lateral posterior choroid artery (Fig 1-104) to distinguish it from the branch of the posterior cerebral artery which runs in the velum interpositum to the choroid plexus of the third ventricle and which was called medial posterior choroidal (Mettler, 1940, Fig 70).

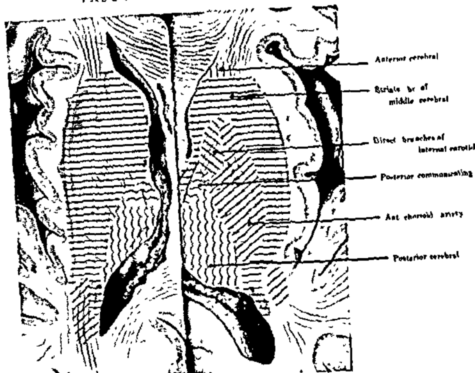


Fig 1-103 Sources of arterial blood supply to the deep masses of the brain (*From Merritt, Mettler, and Putnam, Fundamentals of Clinical Neurology* New York, McGraw-Hill–Blakiston, 1947.)

ANTEROMEDIAL AND POSTEROMEDIAL GANGLIONIC RAMI The perforating branches from the anterior cerebral artery penetrate the olfactory part of the anterior perforated substance, for the most part, and are called anterior central by some authors Mettler speaks of them as anteromedial ganglionic branches (of the circle of Willis) to distinguish them from the posteromedial ganglionic branches of the circle, which arise chiefly from the posterior cerebral artery The posteromedial ganglionic rami run through the posterior perforated substance The anteromedial ganglionic branches supply the septum pellucidum and front of the head of the caudate nucleus The posteromedial ganglionic branches supply most of the ventral part of the thalamus, and also the posterior part of the dorsum of it, as well as the region of the red nucleus and the medial part of the cerebral peduncles

DIRECT BRANCHES OF INTERNAL CAROTID The internal carotid itself gives rise to several small arteries which lie on the tuber cinereum Some of these, the superior hypophyseal vessels, supply the infundibulum and dorsal part of the hypophysis One or more can be traced to the anterior limb of the internal capsule (Fig. 1-103). Occlusion of the direct branch of the internal carotid to the internal capsule results in a characteristic variety of upper *monoplegia* with *facial palsy* If the occlusion is in the dominant hemisphere, the patient is mute The monoplegia is more marked proximally than distally, and the shoulder sags markedly The patient supports the elbow and often protests as though the movement of the arm produced pain As Ecker points out, the preponderance of proximal, as compared to distal, paresis is the opposite of that in cortical lesions

The *anterior choroidal artery* usually arises from the internal carotid In addition to supplying the choroid plexus of the lateral ventricles, it supplies the ventral part of the internal capsule, the lateral part of the subthalamus, and the internal segment of the globus pallidus. It commonly gives rise to the lenticulo-optic artery, noted below

ANTEROLATERAL GANGLIONIC RAMI, THE LENTICULO OPTIC AND LENTICULOSTRIATE ARTERIES. The central branches of the middle cerebral artery are divided, as one passes laterally along the vessel, into (1) one or more longer vessels that lie on or penetrate the optic tract—the

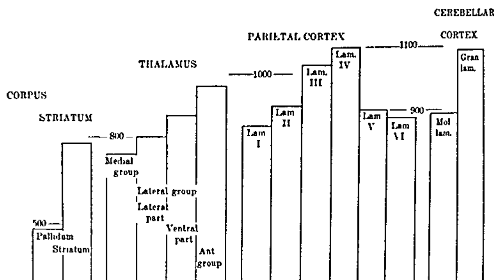


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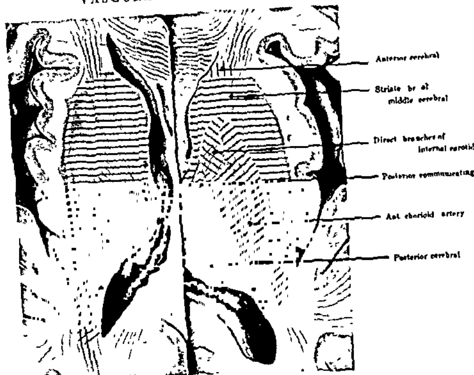


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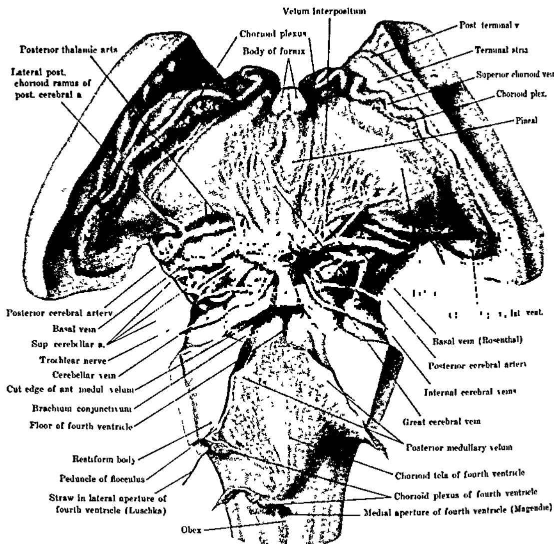


Fig. 1-104. Dorsal surface of the posterior medullary velum and foramina of the fourth ventricle, as seen after removal of the cerebellum The situations of the great cerebral vein and its associated structures are also delineated. (*From Mettler. Neuroanatomy. St. Louis, Mosby, 1948*)

lenticulo-optic arteries (these vessels more frequently arise from the anterior choroidal artery); (2) a group of shorter vessels—the medial lenticulostriate arteries—that penetrate the anterior perforated substance near the lateral olfactory stria (together, these two groups are often called internal striate vessels), and (3) the lateral lenticulostriate (external striate) vessels, which are longer and penetrate its caudal and lateral parts The terminology of these vessels has become confused, not only because variations in the point of origin of these vessels are common, but also because of differences in interpretation of the place at which the internal carotid artery ends (and becomes the middle cerebral). If the end of the internal carotid is taken as the place where it gives off the anterior cerebral, then the above description generally holds good

ARTERIES OF HEUBNER AND CHARCOT. ARTERY OF CEREBRAL HEMORRHAGE. In embryos of up to about 25 mm in crown-rump length, the anterior cerebral artery is represented by a short twiggy projection from the internal carotid. Its stubby branches supply the region just in front of the median telencoele. After the second month, the vessel elongates and moves backward with the developing corpus callosum. The number of branches is reduced, and one, persisting, fuses with a companion of the opposite side to form the anterior communicating artery. Sometimes aberrant branches persist as midline vessels, which can be seen in angiograms. Such "persistent primitive olfactory arteries" may also arise directly from the internal cerebral. One important variation of the branches of the anterior cerebral artery is *Heubner's artery* This arises from the anterior

cerebral just before the anterior communicating. When present, a variable number of the anteromedial ganglionic rami may arise from it. A variety of Heubner's artery, not easy to ... the recurr- ... is ... r-forated substance lateral to the anteromedial ganglionic branches of the *middle* cerebral artery. In this position, it may take the place of the direct branch of the internal carotid to the internal capsule. An important variation occurs in the arrangement of the *perforating* branches of the anterior cerebral.

The term *Charcot's artery* or "artery of cerebral hemorrhage" has been applied to a *lateral lenticulostriate vessel* that arises far laterally and, after passing upward between the lentiform nucleus and claustrum, reaches the rostral and dorsalmost part of the internal capsule. Thus it traverses both the internal and external capsule and never comes near the thalamus. It terminates in the head of the caudate nucleus. Occasionally Heubner's artery follows such a course.

Hemorrhages into the substance of the brain commonly occur in the territories of supply of the lateral lenticulostriate group, the medial lenticulostriate group, and the posterior communicating artery, in this order of frequency (Fig. 1-106). Furthermore, when a vessel begins to fail, the portion of the brain which frequently becomes necrotic is not necessarily coincident with the region of supply but is most pronounced at the periphery of such regions where the head of pressure is lowest.

PERFORATING RAMI OF THE POSTERIOR COMMUNICATING ARTERY. The posterior communicating artery sends a number of branches to and through the medial and lateral eminences of the hypothalamus (Fig. 1-105). These vessels end in the anterior part of the thalamus which they supply. *Internal optic arteries* (of Duret) belong to this group and penetrate the tuberoptic sulcus. The posterior communicating artery is connected with the anterior choroidal by means of an anastomotic ramus (Godinov).

PERFORATING RAMI OF THE POSTERIOR CEREBRAL ARTERY. The posteromedial ganglionic rami of the posterior cerebral artery have been mentioned above, as was the lateral posterior choroid or posterior choroid artery. One or more such vessels arise from the posterior cerebral lateral to the origin of the *posterior communicating* artery and anastomose with the *anterior choroidal* (Fig. 1-100). An anastomosis between the posteromedial ganglionic rami of the posterior cerebral artery and the anterior choroidal artery has been described by *Godinov*.

The posterior cerebral artery moves dorsally; after it has given off its lateral posterior choroid branches, and before the medial posterior choroid artery arises, it sends a number of penetrating vessels into the thalamus just below the pulvinar. These are the *posterior thalamic arteries* (Fig. 1-101). One of these, the thalamogeniculate artery, supplies the region of the pulvinar, geniculate bodies, and posterior limb of the internal capsule. Thrombosis of it is believed to be one cause for the development of the Dejerine-Roussy, or thalamic, syndrome. These arteries are called posterolateral ganglionic vessels by some authors.

Patterns of Vascular Failure in the Central Nervous System. While it is true that the arteries of the ... arteries as end arteries without realizing that they anastomose rather freely outside the brain substance. The arterial circle is itself such an anastomosis, and many similar anastomotic connections exist among the somewhat smaller branches of the circle. The free connection of the anterior choroidal artery with the posterior communicating and with the lateral posterior choroidal and posteromedial ganglionic rami of the posterior cerebral artery are examples of such connections. Anastomoses of this type convert the proximal portions of the interpeduncular vessels into an *interpeduncular plexus* prior to the penetration of these vessels into the interpeduncular substance as the posteromedial ganglionic rami. At levels of smaller magnitude, the existence of a vascular net in the pia and upon the surface of the nervous system has long been recognized, and arterial and venous nets can be found almost anywhere one searches for them in the pia. On gray matter, the meshes of the net are smaller than over white matter. Usually a multitude of small terminal vessels is carried for a short distance into the substance of the nervous system by pial extensions.

The practical significance of such a situation is considerable (Mettler et al.). Obviously it makes a great deal of difference whether a vessel is occluded at its origin prior to becoming involved in contributions to vascular plexuses of the neural surface or afterward, when it has entered the brain.

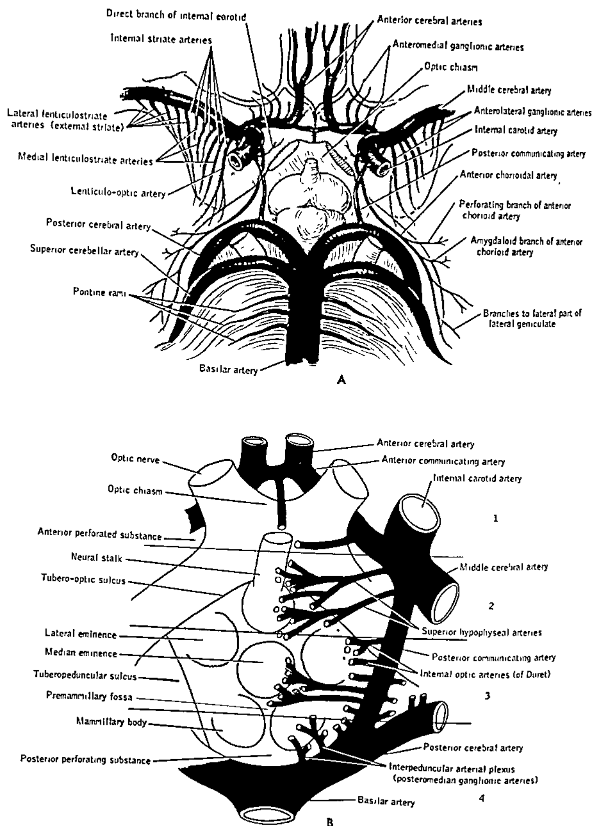


Fig. 1-105. A. Vascular supply of the anterior perforated substance (stippled area). (For a more naturalistic view, see Fig. 1-100.) B. Vasculature of the hypothalamic region, seen from below (according to Bailey). Variations from this pattern are not infrequent. Zone 1, anterior cerebral supply; zone 2, internal carotid supply; zone 3, posterior communicating supply; zone 4, posterior cerebral supply. The stippled area is the topographic region to which the term *tuber cinereum* is applied. (*From Mettler Neuroanatomy. St. Louis, Mosby, 1948.*)

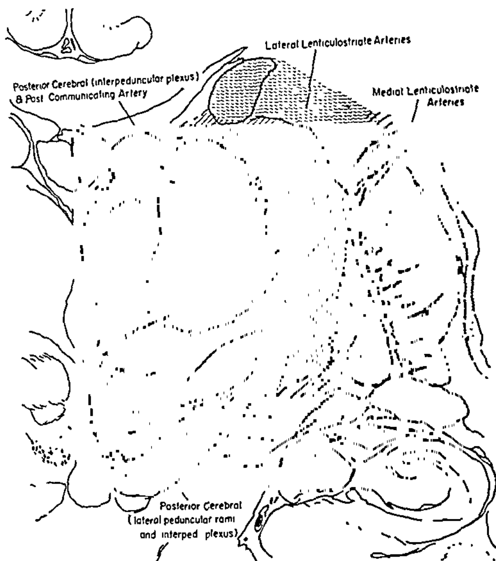


Fig 1-106 Cut surface of brain, showing the distribution of blood from the principal arteries supplying this region Note, in particular, the transition from the territory of the middle to posterior cerebral artery via the posterior communicating artery. *(From Mettler et al. J. Neuropath & Exper. Neurol 1956)*

The common method of determining the area of supply of an artery by injection may give a false impression as to the extent of the ischemia which would develop if the vessel should become occluded Another difficulty that occurs in attempting to predict what area of the neuraxis will be deprived of blood if occlusion develops is the result of local variation in the overlapping of arterial supply between adjacent districts Alexander's dictum that overlapping of areas of supply does not occur is certainly not universally true, for (again choosing the anterior choroidal artery as an example) it is possible to demonstrate that the internal capsule is frequently, if not always, in the normal brain supplied not only by this vessel but also by the posterior communicating artery

The recognition of such local differences in the anatomy of the arterial supply of the brain will go a long way toward explaining the apparent discrepancies in the literature, but it is necessary also to be aware of two other principles if one is to appreciate the significance of apparent discrepancies, not only in the literature but between personally ob-

bral vessels and old, deformed, sclerotic ones.

It is certainly true that the intracerebral capillary and precapillary anastomoses are not of such a magnitude as to provide an efficient collateral circulation in a brain that suffers a sudden, massive arterial occlusion, but it is more than possible that such anastomoses have significant potentialities for shifting a capillary bed of supply from one to another major source of supply if such a shift can take place slowly and over a long period of time.

Injection techniques tell little about these potentialities The study of old diseased brains similarly tends to obscure appreciation of the adaptive potentialities of the healthy vasculature. It is well known that *capsular hemorrhages* occur with great frequency, but it is probably wrong to assume that such hemorrhages are the consequence of the first insult that the brain has suffered Indeed, the general condition of the vasculature of brains showing such hemorrhages suggests that it is only when factors of physiologic safety have been reduced to perilously low levels that isolated vascular insults produce significant clinical signs

Intercommunications between the arteries on the surface of the brain have long been known, as Shellshear pointed out. In spite of this, it has been customary to assume that the area of ischemia produced by ligation of an artery will be more or less identical with the entire region that would be filled by the post-mortem injection of a medium into the vessel at the point of its occlusion Such a pattern may be called "failure in the area of anatomic distribution" If the anatomic pattern is altered as a result of pathologic changes in the vessel under consideration, the principle that the location of ischemia is identical with the area that might have been injected is not altered, the only difference is that one must make allowance for the pathologic condition of the vessel Failure throughout the area of anatomic distribution is, however, very rare. It can develop only when, because of disease or congenital deficiency, overlap or anastomosis is inadequate throughout the entire course of a vessel From a practical point of view, this pattern is probably encountered only following sudden occlusion of very small terminal vessels within the brain or at the point at which they enter it

A second pattern of vascular failure that occurs where overlap is poor and anastomosis deficient is more generalized but is still within the area of [illegible] cular distribution Although less well recognized than the first-described pattern of failure, it is known to occur in certain critical regions, as in the region of the third thoracic spinal cord segment, where there is a shift from the subclavian to the aortic arterial reservoir The role of this pattern of ischemia in facilitating hemorrhage at the border of two zones of primary arterial supply has been elaborated by Zulch (1954), who has also applied the principle to the region of the dorsolateral part of the internal capsule (at the level of the septum pellucidum) and to the cerebral cortex The pattern of failure in areas that lie between territories of primary vascular distribution is likely to develop as a consequence of a generalized reduction in capillary pressure occurring either temporarily (as in a drop in blood pressure) or because of permanent vascular alteration (as in atherosclerosis).

The third possible type of cerebral vascular failure is an ischemia that occurs not in areas where there is little or no collateral vascular supply but where there is more or less overlap or anastomosis Not only are such situations more common than those encompassed in the first two types of vascular failure, but the resulting patterns are apparently less predictable. The great majority of occlusions develop in arteries before they enter the substance of the brain. Therefore, there is a certain amount of opportunity for readjustment in the direction and volume of vascular flow in neighboring anastomotic vessels, provided these have a reasonably normal pattern of distribution and are not themselves the seat of pathologic alterations. In such cases, the ischemic area will be neither between two areas of primary distribution nor coincident with an area of anatomic distribution, but usually will lie in some restricted part of the latter The site will depend upon the nature of the overlap or anastomosis and on the degree of anastomotic confluence, as well as upon the rapidity with which occlusion develops. It is probable that this is the most frequent pattern of vascular failure in the central nervous system, it may be called "subtotal terminal failure."

In summary, vascular failure may occur in the following three regions of the brain (1) the area of anatomic distribution, (2) areas between territories of primary vascular distribution, and (3) part of the terminal area of anatomic distribution The first type of failure can be encountered only in the primary area of distribution of vessels in which, because of congenital deficiency or disease, little or no overlap or anastomosis exists. The second type of failure is encountered along the entire capillary edge of the primary distribution of a vessel which is usually located at a zone of transition where the arterial supply is shifted from one principal source of supply to another. In both the preceding cases, the nature of the ischemic defect can be accurately forecast from a knowledge of the anatomic distribution of the vessel in question The third type of failure, which occurs in the area of distribution of a vessel that has some degree of overlap or anastomosis with another vessel, cannot be accu-

rately foretold by knowing only the anatomic distribution of the vessel It is necessary to know also what anastomotic possibilities exist, and especially what shunts are available and operative Post-mortem material casts some light on the nature of the areas that fail, but since post-mortem examinations are usually conducted in accordance with definite, preconceived frames of reference, failures due to uncomplicated occlusions of vessels may be missed and only those instances picked up in which contributory pathologic changes have resulted in unusually large lesions that produce prominent clinical neurologic signs

ARTERIAL SUPPLY OF THE CEREBELLUM

POSTERIOR INFERIOR CEREBELLAR ARTERY. The course of the posterior inferior cerebellar artery when it arises from the vertebral artery (Fig 1-98) has already been described. Only slightly more frequently does it arise from the basilar artery, either directly or in common with the anterior inferior cerebellar artery. It then passes obliquely and caudally, across the pons and into the pontocerebellar angle If it arises from the rostral part of the basilar, it makes its way dorsally, about the restiform body, to reach the tonsilla If it arises farther caudally, it reaches the tonsilla from the inferior surface of the cerebellum

Once the posterior inferior cerebellar artery reaches the ventral edge of the tonsilla, no matter whence it arose, it gives off a lateral branch, which supplies the surface of the tonsilla and a variable amount of biventral lobule (when the lateral branch is thin and tortuous this part of the biventral lobule is supplied by a variable middle inferior cerebellar artery), and a medial branch, which continues in the sulcus between the vermis and hemisphere

Just before reaching this sulcus the *medial* branch gives off two choroidal rami, one of which is distributed to the medial and the other to the lateral part of the choroid tela of the fourth ventricle. The latter supplies the choroid plexus in the lateral recess of the fourth ventricle, the former runs to the *longitudinal choroid plexus* (of Duret) of this ventricle. The main part of the medial branch of the posterior inferior cerebellar artery next gives off a twig to the nodulus and uvula and a deep branch that proceeds along the posterior medullary velum to supply the caudal part of the bed of the deep nuclei of the cerebellum After reaching the sulcus between the hemisphere and vermis, the medial branch terminates by dividing upon the immediately adjacent, hidden cerebellar cortex. It does not have any appreciable arborization upon the visible portions of the vermis or hemisphere.

MIDDLE INFERIOR CEREBELLAR ARTERY. When the posterior inferior cerebellar artery is small (as it generally is when it arises from the vertebral artery) the basilar may give off, as soon as the vertebrals fuse, a variable middle inferior cerebellar artery. This may originate from the anterior inferior cerebellar, it usually supplies any of the above-mentioned areas not covered by a posterior inferior vessel which may be rudimentary.

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MIDDLE CEREBELLAR ARTERY OF FOIX. This term is sometimes applied to one of the pontine arteries which, after arising from the basilar, bifurcates about the root of the trigeminal nerve (see Fig 1-99) and supplies a small part of the vermis and adjacent medial portion of the cerebellar hemisphere

SUPERIOR CEREBELLAR ARTERY. The superior cerebellar artery is larger than the posterior inferior or anterior inferior cerebellar arteries, with the terminal branches of both of which it anastomoses. It usually arises directly from the basilar artery at the upper border of the pons and passes laterally along the pons, between the trochlear and oculomotor nerves When it arises in this way, it is possible to consider the superior cerebellar and the posterior cerebral arteries as terminal bifurcations of the basilar.

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A second pattern of vascular failure that occurs where overlap is poor and anastomosis deficient is more generalized but is still within the area of anatomic distribution, though *limited to the area of terminal supply*. It may be characterized as "failure in areas that lie between territories of primary vascular distribution." Although less well-recognized than the first-described pattern of failure, it is known to occur in certain critical regions, as in the region of the third thoracic spinal cord segment, where there is a shift from the subclavian to the aortic arterial reservoir. The role of this pattern of ischemia in facilitating hemorrhage at the border of two zones of primary arterial supply has been elaborated by Zulch (1954), who has also applied the principle to the region of the dorsolateral part of the internal capsule (at the level of the septum pellucidum) and to the cerebral cortex. The pattern of failure in areas that lie between territories of primary vascular distribution is likely to develop as a consequence of a generalized reduction in capillary pressure occurring either temporarily (as in a drop in blood pressure) or because of permanent vascular alteration (as in atherosclerosis)

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Once the posterior inferior cerebellar artery reaches the *ventral edge* of the tonsilla, no matter whence it arose, it gives off a lateral branch, which supplies the surface of the tonsilla and a variable amount of biventral lobule (when the lateral branch is thin and *tortuous* this part of the biventral lobule is supplied by a variable middle inferior cerebellar artery), and a medial branch, which continues in the sulcus between the vermis and hemisphere

Just before reaching this sulcus the medial branch gives off two choroidal rami, one of which is distributed to the medial and the other to the lateral part of the choroid tela of the fourth ventricle The latter supplies the choroid plexus in the lateral recess of the fourth ventricle, the former runs to the *longitudinal choroid plexus* (*of Duret*) of this ventricle The main part of the medial branch of the posterior inferior cerebellar artery next gives off a twig to the nodulus and uvula and a deep branch that proceeds along the posterior medullary velum to supply the caudal part of the bed of the deep nuclei of the cerebellum After reaching the sulcus between the *hemisphere* and vermis, the medial branch terminates by dividing upon the immediately adjacent, hidden cerebellar cortex. It does not have any appreciable arborization upon the visible portions of the vermis or hemisphere.

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SUPERIOR CEREBELLAR ARTERY. The superior cerebellar artery is larger than the posterior inferior or anterior inferior cerebellar arteries, with the terminal branches of both of which it anastomoses It usually arises directly from the basilar artery *at the* upper border of the pons and passes laterally along the pons, between the trochlear and oculomotor nerves When it arises in this way, it is possible to consider the superior cerebellar and the posterior cerebral arteries as terminal bifurcations of the basilar.

Sometimes (Fig. 1-99) it arises from 2 mm to 1 cm farther caudally, when it has to be regarded as a basilar branch, and the basilar is considered to have an extent beyond its origin. Regardless of the manner of origin, the superior cerebellar artery divides, just rostral to the trigeminal nerve, into the usual medial and lateral groups of rami The former make their way about the brachium conjunctivum One or more go to the mesencephalon, and the remainder pass rostrally along the side of the central lobule of the vermis to curve over the ventral edge of the superior cerebellar surface. These branches supply the medial half of the superior cerebellar surface and the declive, lobulus simplex, culmen, central lobule, and lingula of the vermis A special, deep terminal, or velar, branch of the medial ramus makes its way along the anterior medullary velum to supply the choroidal plexus of the fourth ventricle and the rostral part of the bed of the deep cerebellar nuclei This is the chief source of supply of the cells in these locations

The lateral group of branches follows the brachium pontis, without approaching the brachium conjunctivum, and also curves over the ventral edge of the superior cerebellar surface, but farther laterally than does the medial group. The lateral rami supply the lateral half of the superior cerebellar surface and also the rostral part of the ventral cerebellar surface.

CEREBELLAR CORTEX. The principal cerebellar arteries discussed above give rise to a double arterial plexus The external plexus, in the outer surface of the pia, consists of vessels of from 0 01 to 0 3 mm in diameter, does not penetrate into the incisuras or sulci, and has rather infrequent anastomoses From the external plexus a large number of branches (0.03 to 0.05 mm in diameter) arise and form an internal plexus, which follows the surface of the cerebellar folia very closely and, in turn, gives rise to superficial and deep branches These branches send blood to the cerebellar cortex by a dual route, consisting of (1) superficial branches that form a primary capillary plexus, located in the molecular layer, and a smaller, secondary plexus, in the granular layer; (2) deep branches of the surface arteries These stout twigs run directly through the cortex (usually in the depth of the sulci), and upon reaching the white matter, the deep branches reascend within the folia and break up into a capillary network in the granular layer. The capillaries of the molecular layer have a finer caliber than those in the granular layer, and the two sets of capillaries anastomose in the granular layer.

Arterial Supply of the Deep Structures of the Midbrain. The arterial supply of the base and tegmentum of the mesencephalon is derived from the superior cerebellar, posterior cerebral, posterior communicating, and anterior choroidal arteries.

SUPERIOR CEREBELLAR ARTERY. In discussing the arterial supply of the cerebellum we have already become familiar with the origin and course of the superior cerebellar arteries. As these lie in the superior pontine sulcus, they give off three or four interpeduncular rami, which, with vessels from the posterior cerebral artery, form the interpeduncular plexus. This, in turn, sends its rami into the posterior perforated substance. As the superior cerebellar artery courses over the crus cerebri, it gives rise to two or three peduncular rami, which penetrate directly into the crus cerebri. The artery now divides into the medial and lateral groups of rami previously noted in the description of the arterial supply of the cerebellum. At least one of the medial rami, the so-called "inferior collicular artery," is distributed to the lateral and dorsal aspects of the level of the inferior colliculus. This ramus sends filaments into the mesencephalon, dorsal and ventral to the lateral lemniscus, passes internal to the trochlear nerve, and ramifies upon the surface of the inferior colliculus.

POSTERIOR CEREBRAL ARTERY. Prior to the origin of the posterior communicating artery, the posterior cerebral artery gives rise to two or three tufts of medially directed vessels, which anastomose with the interpeduncular rami of the superior cerebellar artery and help to form the interpeduncular plexus already noted Where the posterior cerebral artery swings dorsally, between the pulvinar and superior colliculus, and just before the posterior choroidal ramus is given off from it, it commonly gives rise to a branch, the superior collicular artery to the upper part of the tectum.

POSTERIOR COMMUNICATING ARTERY. Close to the junction between the posterior cerebral and posterior communicating arteries the latter gives rise to a variable number of fine, lateral rami to the basis pedunculi One, the middle collicular artery (of Duret), runs entirely

across the basis pedunculi, supplying numerous rostral and caudal twigs to the basis, and then sweeps about the side of the mesencephalon to the quadrigeminal plate. The posterior cerebral also gives off many rostrally and caudally directed collaterals to the basis pedunculi as it runs laterally across it The rostral half of the posterior communicating artery lies too far forward to contribute materially to the blood supply of the mesencephalon

ANTERIOR CHOROIDAL ARTERY. The anterior choroidal artery, which originates from the internal carotid, just before it becomes the middle cerebral, lies for a short part of its course between the basis pedunculi and the optic tract, and gives rise to from three to six twigs which penetrate the rostral part of the basis mesencephali.

INTERNAL VASCULAR ARRANGEMENTS IN THE MESENCEPHALON Cross sections of the mesencephalon reveal that the above-mentioned arteries form a complicated net about it The interpeduncular plexus gives rise to the central arteries of the mesencephalon There are from six to eight of these on each side of the midline The vessels of the right and left sides are usually somewhat asymmetric They pass dorsally into the central gray matter and then suddenly swing laterally, dorsal to the trochlear and oculomotor nuclei Somewhat medial to the mesencephalic root of the trigeminus, they turn up into the quadrigeminal lamina. Throughout their course they give off short, laterally directed rami, which supply the mesencephalic tegmentum

The interpeduncular plexus also gives rise to shorter arteries that penetrate all surfaces of the lower part of the interpeduncular fossa These vessels send their arborizations in a dorsolateral direction to supply the red nucleus and medial edge of the substantia nigra and the tracts in their vicinity, especially the decussation of the brachium conjunctivum. Some five to seven so-called "oculomotor arteries," small branches of the interpeduncular plexus, follow the oculomotor rootlets into the mesencephalon These vessels end in the tegmentum before reaching the oculomotor nuclei, which are supplied by the central arteries These central arteries are too variable to allow one to lay down any general plan of correlation between them and particular parts of the oculomotor complex.

The basis pedunculi is supplied by lateral arteries which arise from the sources already noted and which terminate in the capillary rete of the substantia nigra

The various collicular arteries, however, not only supply capillary networks in the superior and inferior colliculi and region of the lateral spinothalamic fasciculus, but also reach beyond to supply the dorsolateral part of the mesencephalic tegmentum. The collicular capillary nets are reinforced by the central arteries

Although all the mesencephalic capillary networks are essentially continuous, the region supplied by one or another perforating lateral or central mesencephalic vessel becomes necrotic if that vessel is occluded.

Arterial Supply of the Deep Structures of the Pons. The pons receives its blood from vessels that emanate either directly from the basilar artery or from basilar rami destined for more distant structures, such as the cerebellum Some of the former class of vessels enter the medial part of the pons, immediately after originating from the basilar. These are the central (or posterior) pontine arteries, of which there are two sets (Sterzi), one to either side of the midline. The most medial central arteries of the two sides communicate across the midline by means of a delicate net. Others, which originate directly from the basilar artery by one or several small offsets, constitute the lateral or peripheral pontine arteries From 10 to 16 lateral pontine rami ultimately reach the lateral part of each side of the pons The most caudal of these rami run somewhat obliquely caudally and give off twigs that penetrate the foramen cecum and inferior pontine sulcus, anastomosing with an arterial rete that surrounds the medulla oblongata.

The central pontine arteries ordinarily supply not merely the pons Varolii but also the pontine tegmentum. They pass dorsally, just lateral to the midline, and upon reaching the floor of the fourth ventricle, turn laterally. Ordinarily only the ventrolateral and lateral parts of the pontine tegmentum are supplied by the lateral pontine rami and all the remainder of the pons is supplied by the central pontine branches. It is not unusual for some central rami to arise from the proximal portion of the lateral pontine arteries, rather than from the basilar itself, and occasionally they arise from a common trunk that runs parallel to the basilar artery and at its side. It is unusual for the central pontine arteries of the

two sides to be of the same magnitude and symmetrically arranged.

The branches of the anterior inferior cerebellar and labyrinthine arteries, which help to supply the pons, have an arrangement and distribution similar to those of the lateral pontine rami. The posterior inferior cerebellar artery commonly supplies the pons only when it originates from the anterior inferior cerebellar or basilar arteries, instead of from the vertebral. The superior cerebellar artery gives off oral rami to the mesencephalon and caudal rami to the rostral edge of the pons. A small arterial ramus also reaches the pons over the trigeminal nerve. This comes from the arterial supply to the semilunar ganglion.

The pontine vessels anastomose rather freely over each side of the pons but only sparsely across the midline. There is practically no communication with the vascular net of the cerebellum, but rostrally and caudally, the intrapontine twigs anastomose with those of the cerebral peduncles and medulla oblongata. From the pontine net a number of additional offsets run into the substance of the pons. These so-called "special" pontine arteries of Sterzi follow the course of the trigeminus into the pons and supply its nuclei They are not, however, the exclusive supply of these nuclei

Arterial Supply of the Deep Structures of the Medulla Oblongata. The arterial supply of the medulla is entirely derived from the vertebral arteries (Fig 1-97). Having penetrated the posterior atlanto-occipital ligament and sent a few twigs to it and to the membranes inside the vertebral canal, and having given off a nutrient artery to the atlas, the *vertebral artery* perforates the dura mater and sends a few small branches to this meninx. Once inside the subarachnoid space, the vertebral arteries converge across the ventral surface of the medulla, medial to the rootlets of the hypoglossal nerve, and unite just caudal to the inferior pontine sulcus and at an angle of from 50 to 78° (usually 60°).

Just before the vertebral artery passes beneath the upper part of the denticulate ligament, it gives off two branches, one of which is generally larger than the other. These branches course dorsally over the ligament between its origin and second insertion The smaller and more caudal one is the posterior spinal artery, the larger and more rostral is the posterior inferior cerebellar.

The *posterior spinal artery* passes between the filaments of the spinal portion of the accessory nerve and between the roots of the first and second cervical nerves. It then runs caudally along the dorsal surface of each side of the cord. As the posterior spinal artery approaches the lower border of the medulla, it gives off an ascending ramus, which is distributed along the caudal part of the posterior intermediate sulcus of that structure.

The *posterior inferior cerebellar artery* may arise from either the vertebral or the basilar artery. (Cases of either origin are of about the same frequency.) In the former case, it may take its origin in common with the posterior spinal artery, as noticed above, or it may not arise until much later, i e., more rostrally. It gives off a descending ramus, which is distributed along the rostral part of the posterior intermediate sulcus of the medulla. The posterior inferior cerebellar artery reaches the dorsal surface of the restiform body by passing between some of the offsets of the ninth to eleventh cranial nerve complex and arrives at the ventral surface of the tonsilla.

The next branch of the vertebral is the *anterior spinal artery* (Fig 1-99) This vessel originates from the medial side of the vertebral, at a level corresponding to the middle of the inferior olive, turns mediocaudally on the ventral surface of the cord, and fuses in the midline with its fellow of the opposite side at a level near the lower end of the inferior olive The fused artery, also called *anterior spinal*, courses caudally at the bottom of the ventral median fissure of the cord and is reinforced by the arteries that run into the cord along the nerve roots in the manner already described Before fusing with its fellow, the anterior spinal artery gives rise to a number of branches that supply the ventral part of the medulla, over which it passes. The area of the ventral medullary surface that lies rostral to the anterior spinal arteries and within the angle of the two vertebrals is supplied by medullary rami that arise from the medial aspects of both vertebrals

The ventral part of the superficial arterial net that is produced by the above vessels gives rise, in the caudal part of the medulla, to a single artery, the *perforating central artery of the medulla* (median artery of Duret), and, in the more rostral portion, to two penetrating arteries (Adamkiewicz's arteries of the ventral

median medullary fissure), one on either side of the median raphe. In the lower part of the medulla, the central arteries alternately turn toward first one and then the other side of the central gray matter. At the pyramidal decussation, the central arteries supply only the substance of the decussation, but at the level of the inferior olives, they pass through the medulla to the floor of the fourth ventricle, where they supply the hypoglossal nuclear complex and dorsal motor nucleus of the vagus.

The rest of the medulla is supplied by peripheral arteries that penetrate its substance like the spokes of a wheel, but much more irregularly. Some are thicker than others, some are long, others short. Below the obex, the nucleus of the solitary fasciculus and the commissural and dorsal motor nuclear complex of the vagus are supplied by the artery of the posterior median fissure, which corresponds to the anteriorly located central artery. The ambiguous nucleus and, to some extent, also the vagal dorsal motor nuclear and hypoglossal complex receive peripheral vessels that reach them by following the general direction of the intramedullary courses of the cranial nerves, though not necessarily accompanying them. The hypoglossal and dorsal motor complexes thus receive a dual blood supply, and so do [illegible]

[illegible], the arteries that supply the portion of the spinal cord lying within any given vertebra are whichever arteries come into closest association with the neighboring intervertebral foramina. Proceeding caudally they are the vertebrals, the ascending cervical branches of the inferior thyroid, the deep cervical branch of the costocervical trunk (Fig. 1-95A), and the intercostal, lumbar, iliolumbar, and lateral sacral arteries (Fig. 1-95B). The single offset that the appropriate artery sends into the intervertebral foramen is called a *lateral spinal artery*. The lateral spinal arteries passing into the intervertebral foramina of the lower cervical and upper thoracic vertebrae and supplying the cord segments C7 to T2 are especially variable. This is a site of frequent vascular abnormalities, assumed to be due to imperfect anastomosis between the lateral spinal arteries derived from these various, somewhat independent, sources. The nutrient arteries to the vertebrae have usually been given off before the lateral spinal artery approaches the intervertebral foramen. The lateral spinal artery sends dorsal and ventral endorachitic rami to the periosteum of the vertebral canal and, just before entering the dura, gives off dorsal and ventral dural rami. Once inside the dura, it contributes several small rami to the mixed nerve, and splits into dorsal and ventral radicular arteries of unequal size, which accompany the corresponding roots. Moreover, the magnitude of the radicular arteries of either category also varies greatly, so that if one examines all the ventral roots of one side of the cord, one can rarely find more than from four to ten large vessels (at least one in the cervical, two in the thoracic, and one in the lumbar region). The largest of these, the great ventral radicular artery, is usually found on the left, between the eighth thoracic and third lumbar roots. Two such vessels may be present in this area. Another large, ventral radicular artery is usually found in association with the last cervical or first thoracic ventral root. The dorsal radicular arteries are generally smaller than the ventral, but more of them (about 35) are completely developed. The largest dorsal radicular arteries usually run in relation to cord segments other than those receiving the largest ventral radiculars.

The ventral radicular artery runs along the ventral edge of the ventral root, which it supplies, crosses the ventral surface of the spinal cord, and runs to the ventral fissure. Just before reaching the fissure, it bifurcates into rostral and caudal rami, which fuse with their fellows of the opposite side to form a single, unpaired *anterior spinal artery* (of Adamkiewicz, anterior medial spinal artery), which is bound by pia against the ventral fissure. The upper cervical part of the anterior spinal artery arises by the convergence of two or more unequal anterior spinal branches of the prebasilar parts of the vertebrals. These branches commonly unite in the vicinity of the junction between the second and third cervical segments. The caudal end of the anterior spinal artery composes the terminal artery, which runs along the filum terminale.

Each centimeter of the anterior spinal artery

[2] Space for the pictorial illustrations of this section is unavailable. The reader is referred to the illustrations in the author's *Neuroanatomy*, 2d ed., St Louis, Mosby, 1949.

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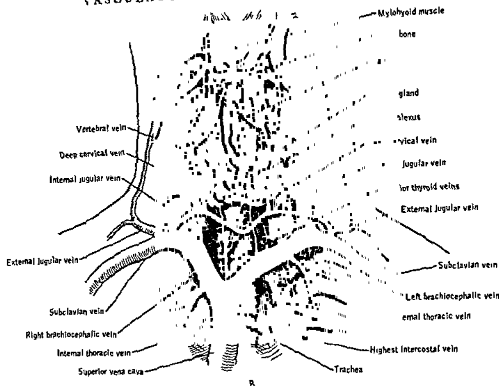


Fig 1-107. Venous drainage of the head A. Position of the internal jugular vein and its tributaries B Position of the brachiocephalic veins and their tributaries. *(From Mettler. The Medical Sourcebook Boston, Little, Brown, 1959, after Henle)*

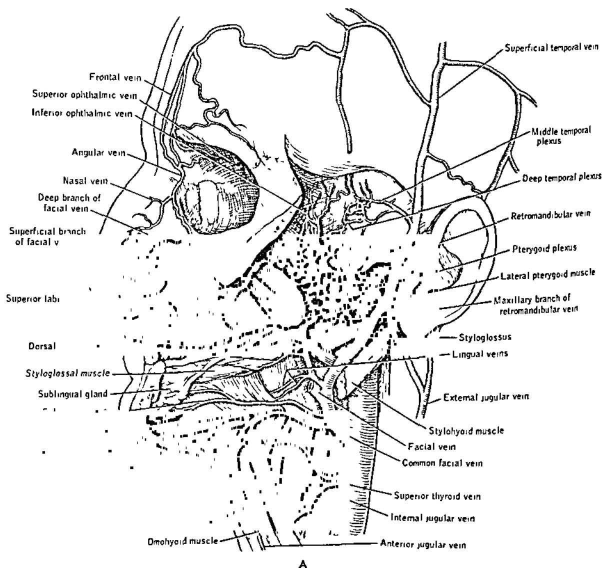
artery), which lies in the posterior lateral sulcus just medial to the line of entrance of the dorsal roots The anterior branches of the posterolateral spinal arteries anastomose with filaments from the anterolateral spinal artery, and these loops of communication are further interconnected by a longitudinally directed artery, the lateral spinal artery, which lies in the substance of the denticulate ligament On the conus medullaris, the posterolateral spinal arteries, which do not continue into the filum, communicate with the terminal portion of the anterior spinal by means of the *arched anastomotic branch* (of Kadyi), which is dorsally concave

The elaborate surface system of vessels just described transforms the spatially intermittent, segmental inflow into a reasonably uniform flow to the periphery of the cord and reduces the hazard that must attend obstruction of a particular part of the peripheral supply The vessels arising from the surface plexus and penetrating the substance of the cord in a radial manner are collectively called peripheral arteries, since they supply the white matter. One of these, the *dorsomedian artery*, accompanies the median septum and supplies the posterior gray commissure as well as the base of the dorsal gray columns. Individual dorsomedian arteries may not be so long The *intermediate septal artery* accompanies the posterior intermediate septum It may also supply the posterior gray commissure and base of the dorsal gray column. The artery of the dorsal root accompanies the incoming fibers of that structure, supplies a branch to the substantia gelatinosa, and then proceeds to the region of the central canal, it is the most usual supply of the posterior intermediate septum and adjacent part of the dorsal gray column There are three other significant peripheral arteries One of these, the *median lateral spinal artery*, arises from the lateral spinal artery and supplies the dorsomedial third of the lateral funiculus In the medial part of the lateral funiculus, it anastomoses with the branches of the sulcal artery that supply the ventral gray column. Midway between the median lateral artery and the dorsal root, the *dorsolateral spinal artery* (a deep ramus, not to be confused with the super-

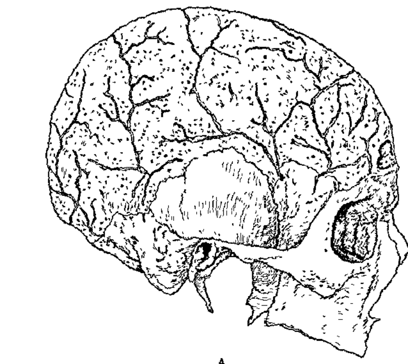
commonly gives rise to from three to four dorsally directed vessels, the *ventromedian or sulcal arteries,* which pass dorsally into the ventral fissure and are directed, alternately, into either side of the central gray matter, of which they are the sole source of blood. Occasionally, a single ventromedian artery will split in two and be distributed to both sides of the central gray matter.

The anterior spinal artery also gives off laterally directed rami, which form an anterior arterial plexus on the ventral surface of the cord, the lateral border of which forms a longitudinal channel, the *anterolateral spinal artery.* This artery lies just between the fascicles of the ventral roots, as they emerge from the cord, and is reinforced by offshoots from the ventral radicular artery.

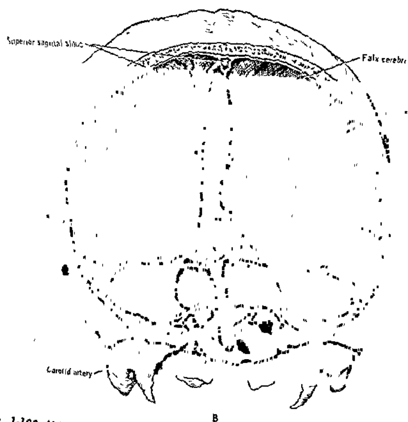
The *dorsal radicular artery* courses along the ventral surface of the dorsal root, to which, as well as to the dura, it contributes nutrient twigs; upon reaching the insertion of the dorsal roots, it divides into rostrally and caudally directed branches, which unite with the vessels of the adjoining segments to form a *posterolateral spinal artery* on each side of the dorsum of the cord. The posterolateral spinal artery lies just lateral to the insertion of the dorsal root and gives rise to anterior and posterior branches. The latter are very fine and run medially between the filaments of the nerve roots. They form the *posterolateral arterial plexus* (or coronal rami of the posterior spinal arteries), which lies between the dorsal nerve roots of the two sides. The elements of this plexus are interconnected, laterally, by means of a longitudinal vessel, the *posterior spinal artery* (Adamkiewicz's posterior vertebrospinal



A



A



B

Fig. 1-108 Veins of the cranial vault. A. Diploic veins. B. Venous sinuses in the posterior half of the cranial vault. (From Mettler. The Medical Sourcebook. Boston, Little, Brown, 1959, after Henle.)

ficial posterolateral spinal artery) enters the cord, supplies the dorsal third of the lateral funiculus, and anastomoses, in the medial part of the lateral funiculus, with the branches of the sulcal artery which supply the posterior gray column. Lastly, several *ventrolateral (peripheral) arteries* enter the cord along the filaments of the ventral roots. They supply the ventral third of the lateral funiculus and the lateral half of the ventral funiculus. The medial half of the ventral funiculus is supplied by lateral offshoots from the sulcal arteries.

The *sulcal arteries* supply a rostrocaudal, spindle-shaped area of appreciable size. The area of distribution of an individual, peripheral artery has the shape of a cone with its base in the surface of the cord Within the cord there is relatively little intercommunication between branches of different peripheral arteries.

VEINS OF HEAD AND NECK

The venous system of the head and neck resembles the arterial system but is represented by a greater number and variety of channels, which, moreover, are more variable than the corresponding parts of the arterial system. The principal channels of passage of blood from the head to the base of the neck are the *internal* and *external jugular veins* and the *vertebral venous plexuses* The channel of passage from the upper extremity to the root of the neck is the *subclavian vein*. On both sides of the body, these vessels unite in a *brachiocephalic* (old term, innominate) *vein*. These fuse in the thorax to form the superior vena cava.

Superficial. The venous drainage of the front of the head is carried by the *facial* (old term, anterior facial and, also, common facial) *vein* and the *retromandibular* (old term, posterior facial) *vein*, which joins it just before it drains into the internal jugular vein The posterior part of the head drains into the external jugular vein.

The facial vein (Fig 1-107A) originates near the inner canthus of the eye where the supratrochlear (old term, frontal), supraorbital, and angular branches of the facial vein communicate with the nasofrontal, ethmoid, and lacrimal branches of the superior frontal vein. Sometimes the angular vein communicates with the inferior ophthalmic (Fig. 1-109).

The facial vein passes downward across the face near the anterior border of the masseter muscle, passes backward over the submaxillary gland, and, uniting with the deep portion of the retromandibular vein, passes beneath the anterior margin of the sternocleidomastoid muscle to join the internal jugular vein beneath the anterior border of the sternocleidomastoid. It may join either the anterior or the external jugular vein. The facial vein receives a tributary, the *deep facial vein*, this tributary arises in the pterygoid venous plexus, which is associated with the lateral pterygoid muscle and which, in turn, receives the vein of the pterygoid canal and the middle meningeal veins. The facial vein has no valves, and because it lies among muscles, the direction of its blood flow may be easily altered. Because it drains an area of the face that is frequently the site of infections, and because it communicates with the cavernous sinus, its clinical importance is appreciable. It will be perceived from the preceding description that the facial vein communicates with the cavernous sinus at both its origin and its termination. Through its angular branch the facial vein communicates with the superior ophthalmic vein. Through the deep facial, it communicates with the pterygoid plexus, and through the emissaries of the pterygoid plexus, with the cavernous sinus.

The *retromandibular vein* drains the area supplied by the superficial temporal artery, passes through the parotid gland, and divides into two parts. the superficial portion joins the external jugular vein, and the deep portion joins the facial vein

The *anterior jugular vein* (Fig 1-107) begins above as a communication from the facial vein, extends downward along the anterior margin of the sternocleidomastoid muscle, and joins the internal jugular vein behind the sternoclavicular joint. Usually this vein is small, but sometimes it is large and may be mistaken for the internal jugular It is the superficial vessel that bleeds when the throat is cut

The *lingual vein* passes backward across the carotid sheath to join the internal jugular vein. It may receive the superior thyroid vein and vena comitans of the hypoglossal nerve, or these veins may join the internal jugular directly

Deep. The deep veins of the neck are (1) the *internal jugular* and its deep branches—a group of veins that drain the trachea, esophagus, thyroid, and other deep cervical structures

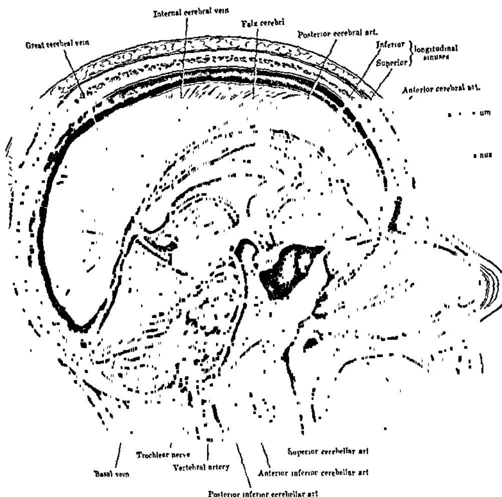


Fig 1-110 Venous sinuses of the falx cerebri (cf Fig 1-109) and their communication with the vein of the foramen cecum The position of the variably present pharyngeal pituitary is indicated The falx cerebri occasionally contains flat bony concretions that show up in roentgenograms Sometimes it is perforated, especially rostrally, where it may appear definitely lacelike. (*From Mettler Neuroanatomy St Louis, Mosby, 1948*)

veins of the ear and, especially, of the orbit communicate to some extent with the venous system of the cranial vault. The pharyngolaryngeal drainage is into the deep veins of the neck

DIPLOIC VEINS The outer and inner tables of the flat bones of the calvaria are separated by cancellous bone In this spongy substance are found four systems of venous channels, the frontal, anterior temporal, posterior temporal, and occipital diploic veins (Fig 1-108A), which begin near the midline of the top of the skull and drain downward These channels in the bone are seen as defects in roentgenograms, the *posterior temporal* channels forming the familiar parietal "star" or "spider."

The *frontal diploic channels* connect the superior sagittal sinus with the supraorbital vein (Fig. 1-109). The *anterior temporal diploic veins* end in the sphenoparietal sinus on the inside of the skull and, externally, in the temporal veins. The *posterior temporal diploic vein* ends in the transverse sinus, which also may receive the occipital diploic vein. Sometimes the latter ends externally in the occipital vein (Fig. 1-109).

VENOUS SINUSES The venous channels of the meninges consist of spaces within the layers of dura that serve as veins. These channels are without muscular walls, are relatively rigid, and are generally found where the dura sends out leaflets from otherwise flat sheets, in free

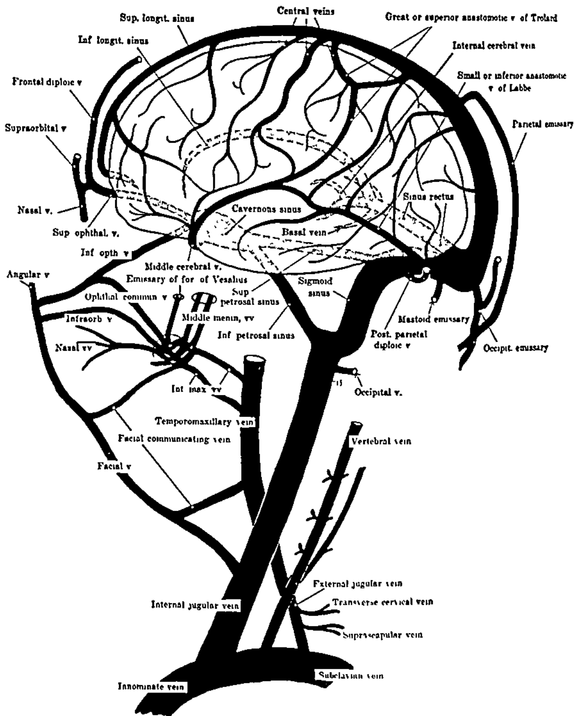


Fig. 1-109. Venous return of the cerebrum and its connections with the vascular channels of the skull. The deep venous arrangements are dotted (cf Fig. 1-110). *(From Mettler. Neuroanatomy. St. Louis, Mosby, 1948.)*

(the deep cervical, inferior thyroid, least thyroid, thymic, tracheal, and esophageal veins), (2) those which form a plexus about and within the vertebral column, (3) the vertebral venous plexuses; and (4) the vertebral veins.

The deep veins of the head are customarily divided into those of the cranial vault and brain, those of special cavities (notably the orbit, nose, and ear), and those of the pharynx and larynx. These veins and the superficial venous drainage of the head and neck converge in the jugular venous system and the vertebral venous system.

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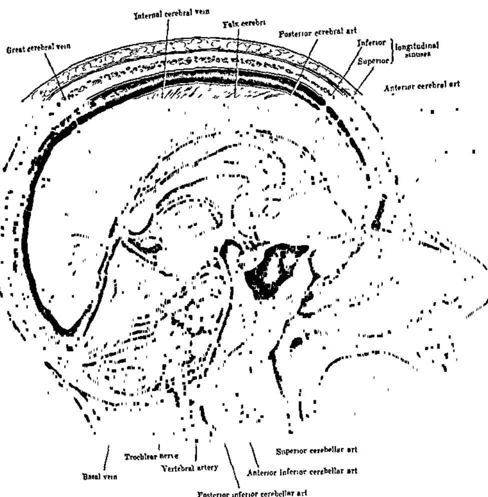


Fig 1-110 Venous sinuses of the falx cerebri (cf Fig 1-109) and their communication with the vein of the foramen cecum. The position of the variably present pharyngeal pituitary is indicated. The falx cerebri occasionally contains flat bony concretions that show up in roentgenograms. Sometimes it is perforated, especially rostrally, where it may appear definitely lacelike (*From Mettler, Neuroanatomy, St Louis, Mosby, 1948.*)

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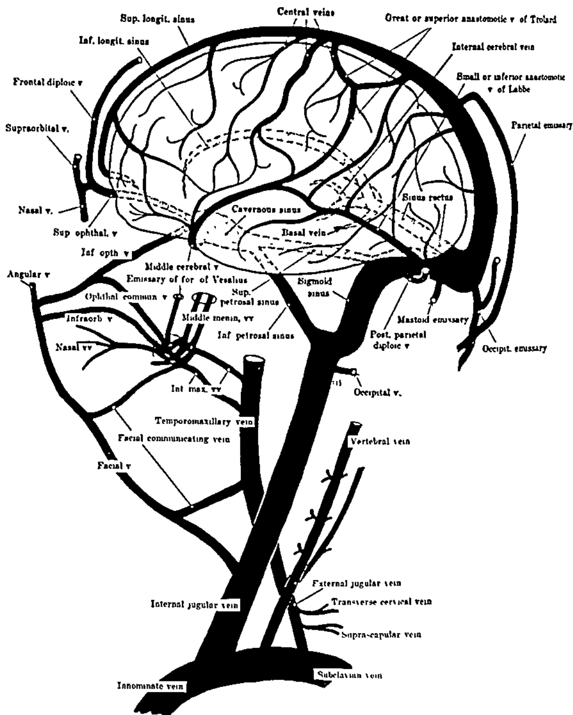


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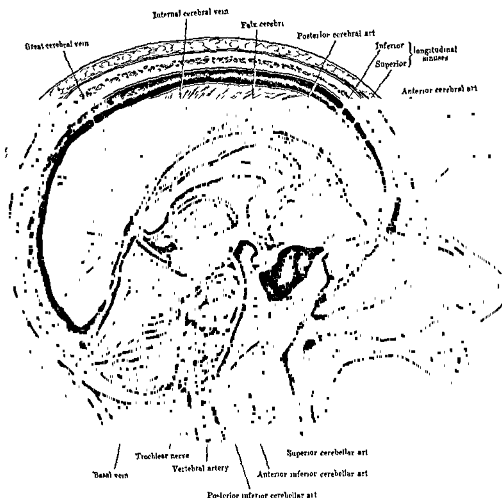


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edges of the dura, or where the dura is applied to bony irregularities or ridges.

Where the tentorium is reflected from the occipital bone, the *transverse sinuses* (old term, lateral sinuses) are found. They run forward and are applied to the groove for the transverse sinus, which may be seen on the inside of the occipital bone (Fig. 1-108B). Where the petrous portion of the temporal bone meets the occipital, the transverse sinus turns abruptly caudally as the sigmoid sinus and emerges through the jugular foramen. Brain abscesses may develop in the region of the petrous and mastoid portions of the temporal bone as sequelae to middle-ear infections. The sigmoid sinus and the eighth cranial nerve may also be involved by aural infections. The relation of the transverse sinus to the external surface of the cranium is important A trephine opening, 2 5 cm posterior to the external auditory meatus and directly behind it, exposes the bend of the lateral sinus. This is the part which most frequently requires exposure after the development of mastoid abscess complications.

The *superior sagittal sinus* is found along the line where the falx cerebri joins the dura of the cranial vault It follows the outer edge of the falx cerebri from the region of the foramen cecum to the transverse sinuses and may drain in various ways, most often it empties into the right transverse sinus The point of union between the superior sagittal and the transverse sinuses is called the *confluence of the sinuses* (or *torcular Herophili*)

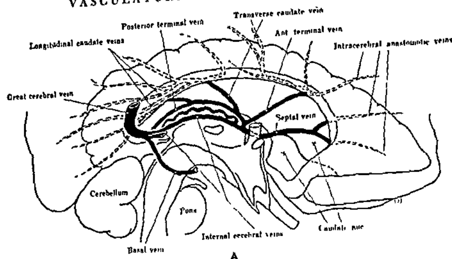
The falx cerebri bears in its lower (ventral) edge the *inferior sagittal sinus* (Fig. 1-110). This channel begins anteriorly just behind the foramen cecum. In front of this point, it may communicate with the superior sagittal sinus. Running backward in the ventral border of the falx, it extends to the point where the ventral border of the falx joins the anterior border of the tentorium

A straight channel, the *sinus rectus*, lies along the line of union of the tentorium and falx cerebri, and therefore in the exact anteroposterior midline. It connects the inferior sagittal sinus with the left transverse sinus in those cases in which the superior sagittal sinus drains into the right transverse sinus The reverse relation may occur. A large vein, the *great vein of the cerebrum (of Galen)*, runs from the brain substance into the point of confluence of the inferior longitudinal and the straight sinuses (Figs. 1-110 and 1-111A).

Running from the point of confluence of the sinus rectus and the transverse sinus to the foramen magnum is a midline reflection of dura represented by a stout band, or series of bands, which incompletely divides the posterior fossa into two halves (Fig 1-108B) This reflection is the falx of the cerebellum, in the base of which is found the *occipital sinus* (Fig. 1-108B).

As the dura is reflected up from the basis cranii to the side of the hypophyseal fossa, a space is formed between the two layers just above the carotid groove This is the *cavernous sinus*, into which the *ophthalmic veins* (Fig 1-109) drain. The cavernous sinuses communicate across the midline through the *intercavernous sinuses* in the sella turcica, and also through the *basilar plexus*, found at the junction of the sphenoid and the basilar part of the occipital bone. The cavernous sinuses communicate posteriorly and, on either side, with the transverse sinuses. This communication is effected through the *superior petrosal sinuses*, lying along the crest of the petrous part of the temporal bone. The cavernous sinuses also communicate with the jugular bulbs (Fig 1-109) by means of the inferior petrosal sinuses, which empty immediately below the opening of the transverse sinus.

EMISSARY VEINS. A number of small veins pierce the skull at various external loci If, after traversing the bone, these veins communicate with the venous sinuses of the dura, they are called emissary veins (Fig 1-109) If an epidural space is formed by a blow upon the head, such a space is very likely to fill with blood because the emissary veins will be torn during the formation of this space The chief emissary veins are the occipital (old term, mastoid) emissary, passing through the mastoid foramen and uniting the transverse sinus with the posterior auricular vein or with an occipital vein, the venous plexus of the hypoglossal canal, passing through the hypoglossal canal and joining the transverse sinus with the vertebral veins and the deep cervical vein, the condyloid emissary vein, which after passing through that canal connects the transverse sinus with the deep cervical veins. It will be observed that all three of these emissary veins connect with the transverse sinus. The emissary of the foramen cecum connects the su-



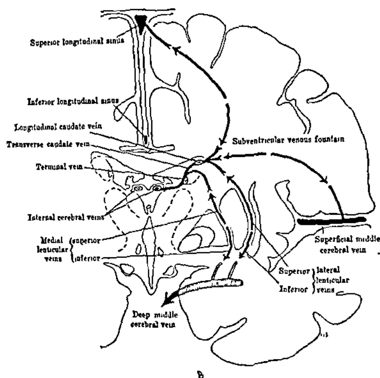


Fig 1-111. A Internal venous channels of the cerebrum. The wavy vessel between the posterior terminal and internal cerebral is the superior choroidal vein B Venous drainage of the brain. Schematic coronal section (cf Fig 1-109). (*From Mettler. Neuroanatomy St. Louis, Mosby, 1948*)

perior sagittal sinus with the nasal veins or veins of the frontal sinus, the parietal emissary passes from the superior sagittal sinus through a parietal foramen and joins the scalp veins. These two emissaries thus go to the superior sagittal sinus The plexus of the oval foramen connects the cavernous sinus with the pterygoid plexus The venous plexus of the internal carotid artery, an emissary plexus passing over that artery, connects the cavernous sinus with the internal jugular by way of the pterygoid plexus Another important venous anastomosis is through the veins of the orbit with the angular veins.

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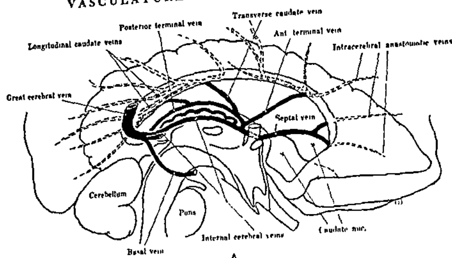
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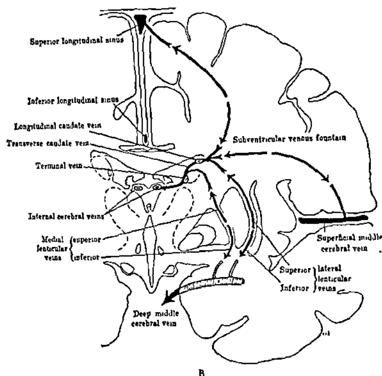


Fig 1-111. A Internal venous channels of the cerebrum The wavy vessel between the posterior terminal and internal cerebral is the superior choroidal vein. B. Venous drainage of the brain. Schematic coronal section (cf. Fig 1-109). *(From Mettler. Neuroanatomy. St. Louis, Mosby, 1948)*

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VENOUS DRAINAGE OF THE CEREBRUM. The interior of the cerebrum and part of its ventral

surface drain into the *basal vein of Rosenthal* and the *internal cerebral veins of Galen*, which converge to form the *great cerebral vein of Galen*, which empties into the sinus rectus. The basal vein of Rosenthal (Fig. 1-111A) belongs to part of the superficial group of cerebral veins, but the internal cerebral veins and their tributaries compose the deep group of cerebral veins (Fig. 1-112). The former group will be considered first

Superficial Group of Cerebral Veins (Fig. 1-109) The superficial group of veins can be easily seen on the surface of the cerebrum. On the dorsal surface, a large number of superior cerebral veins empty into the *superior sagittal sinus* through openings in the sinus called "venous lacunae." As a result of this arrangement, the arterial and upper venous channels carry blood in the same direction The superior cerebral veins drain the dorsal, dorsolateral, and medial two-thirds of the brain All empty into the superior sagittal sinus In the newborn, they enter the sinus individually, in the adult, each vein on the medial surface first communicates with a lateral vein before entering the sinus. Since there are from 12 to 15 lateral and only 8 to 10 medial veins, some of the former enter the sinus alone

As the *superior cerebral veins* travel to the superior sagittal sinus, they must cross abou a millimeter of subdural space, which is continued down the side of the falx cerebri and between it and the arachnoid In bridging th gap, they are surrounded by a cuff of connec tive tissue attached on the one side to the dur and on the other to the leptomeninges. Th cuff becomes denser with age and as the fal cerebri stiffens.

The *inferior cerebral veins* are divided int orbital cerebral, middle cerebral, and occipit cerebral veins. The orbital cerebral veins, thre to seven in number, are small and drain onl the rostral tip of the supraorbital cortex. The empty into the rostral end of the superi sagittal sinus. The major portion of the supr orbital cortex is drained mediocaudally into th basal vein, further discussed below.

The *middle cerebral veins* consist of th superficial middle cerebral (or Sylvian) ve and a deep middle cerebral vein (or vein the insula). The former, apparent on the su face of the brain, lies among the trabeculatio of the arachnoid. It arises in the central pa of the lateral surface of each hemisphere b the confluence of three or four tributaries an as it passes ventrally, receives additional trib

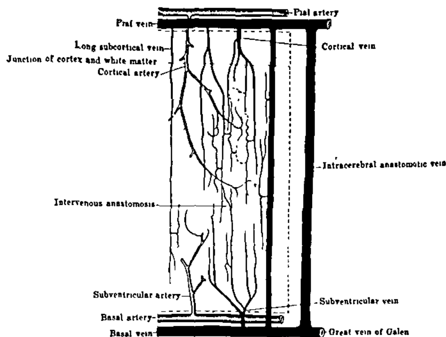


Fig. 1-112. Diagram of the venous circulation of the white matter and of the anastomotic communications of the superficial and deep venous drainage (*From Mettler, Neuroanatomy, St. Louis, Mosby, 1948, after Schlesinger.*)

taries At the base of the cerebrum, it crosses the subdural space, penetrates the dura mater, where it has the character of a sinus, and then either empties into the cavernous sinus or turns backward toward the base of the petrous part of the temporal bone and drains into the superior petrosal sinus. At its upper, or dorsal, end the *superficial middle cerebral vein* is generally connected with the superior longitudinal sinus by means of the *great or superior anastomotic vein of Trolard*, which passes ventrally among the roots of the middle cerebral vein, then courses caudally, and, finally, passes rostrally to join the superficial middle cerebral vein just before this empties into the sinus In this way, a direct connection between the sinuses of the base and vault is established. Another, similar connection exists in the lesser *inferior or posterior anastomotic vein of Labbé*, which runs between one of the posteriorly located superior cerebral veins, or the superficial middle cerebral vein, and one of the occipital veins (Fig 1-109). Sometimes it empties directly into the sinus transversus. Either of these anastomotic connections may be absent Another anastomotic channel is the *basal vein of Rosenthal*, discussed below.

The *deep middle cerebral vein* originates from the confluence of tributaries that drain the insula and adjacent parts of the cerebrum. It courses ventrally in the depths of the lateral cerebral fissure to reach the base of the brain Here, it empties into either the superficial middle cerebral or, more frequently, the basal vein As it crosses the anterior perforated substance, it receives a number of delicate veins (rostral elements of the external and internal inferior lenticular venous system, central anterior veins of the anterior perforated area), which drain the lentiform nucleus.

The *occipital veins* are small vessels that arise from the circumferential part of the basal portion of the occipital lobe They may be divided into five or six medial and two lateral occipital veins. The former empty into the superior petrosal sinus, great cerebral, internal cerebral, or basal veins The latter discharge into the horizontal part of the transverse sinus

The *basal vein* originates on either side of the optic chiasm by the confluence of the anterior cerebral (which drains the ventral portion of the medial surface of the frontal lobe) and the deep middle cerebral veins. Passing backward, it receives tributaries from the anterior perforated substance, optic tract (ventral to which it passes), and tuber cinereum. It reaches the basis pedunculi somewhat lateral to the point of emergence of the oculomotor nerve, follows the side of the mesencephalon dorsally, crosses the superior colliculi, and unites with the internal cerebral vein to form (upon confluence with the corresponding structures of the opposite side) the *vein of Galen* (Fig. 1-110). The basal vein must not be confused with the basilar venous plexus.

Deep Group of Cerebral Veins. The deeper parts of the centrum semiovale are drained by intracerebral anastomotic veins. Rostrally, these run into the septal vein of each side. The *septal veins* run across each leaf and, after being joined by the thalamostriatal (old term, terminal veins) and the choroid veins, empty into the *internal cerebral vein* (Fig. 1-111). This lies (Fig 1-104) in the velum interpositum to the side of the third ventricle. The *thalamostriatal veins* drain all of the thalamus and the dorsal part of the lentiform nucleus, and the *choroid vein* of each side drains the choroid plexus of the lateral ventricle In the caudal part of the velum interpositum, the internal cerebral veins of the two sides approximate each other and form the unpaired *great cerebral vein of Galen*, into the ventral surface of which the basal veins empty (Fig. 1-104). The great cerebral vein then receives the superior cerebellar veins and empties into the sinus rectus

VENOUS DRAINAGE OF THE CEREBELLUM. The blood of the bed of the deep cerebellar nuclei is returned by veins that correspond to the arteries These veins differ from the arteries in that they drain a much more extensive area than the latter supply, draining even some of the medullary substance of the arbor vitae.

The veins of the folia are formed by the confluence of a *cortical capillary plexus* into a subpial net, which is most voluminous in the sulci. These nets unite into trunks which ascend in the sulci and, uniting on the surface with others, *form channels* which are partly comparable in nomenclature to the arterial supply but which converge in the opposite direction The superior cerebellar veins are an exception

The *superior cerebellar venous channels* converge into a trunk just dorsal to the inferior colliculus, this common superior cerebellar vein then empties into the internal cerebral veins or into the great cerebral vein of Galen Some-

times one or more of the superior cerebellar venous channels enter the sinus rectus directly.

The *anterior inferior cerebellar veins* are numerous and collect most of the blood from the inferior surface of the cerebellum. They are joined by the lateral veins of the pons, and the united channel converges into the superior petrosal venous sinus.

The *middle inferior cerebellar veins* number from three to six small vessels, which originate from the uvula and posterior medullary velum. They course caudally over the biventral lobule, picking up tributaries en route, sometimes fusing into a single channel and sometimes continuing separately, they terminate in the confluens sinuum or in one of the transverse sinuses.

The *posterior inferior cerebellar veins*, three or four in number, arise from the laterodorsal parts of the inferior surface of the cerebellum and run into the transverse sinus

All the cerebellar veins are interconnected by abundant *anastomoses*

VENOUS DRAINAGE OF THE MIDBRAIN The mesencephalon is drained by central veins (which are larger but fewer than the central arteries) on each side of the raphe, and by numerous lateral veins that radiate peripherally. The position of the central veins is similar to that of the arteries, and they similarly drain into an abundant interpeduncular plexus, the vessels of one side freely communicating with those of the other The veins from the substantia nigra also empty into the interpeduncular venous plexus. There are usually a few lateral veins that emerge with the rootlets of the oculomotor nerve The lateral veins of the mesencephalon drain into the *basal vein of Rosenthal*, which also receives tributaries from the interpeduncular fossa. One of these, which commonly accompanies the middle collicular artery, is the *posterior communicating vein* (of Testut, or vena anastomotica of Charpy), which may be quite large. Often no particular, prominent channel can be distinguished

Instead of pursuing a caudally directed course, one or both basal veins may empty into the *cavernous sinus*. In that case, the *lateral mesencephalic veins*, from the basis pedunculi, drain forward into a vessel which, after receiving tributaries from the interpeduncular venous plexus, represents the corresponding part of the usual basal vein, but in which the blood travels in a direction opposite from the customary one. The lateral mesencephalic veins, issuing from the lateral portion of the mesencephalon, on the other hand, drain into short vessels that empty into the internal cerebral or great cerebral vein. There is, moreover, a conspicuous *vein of the trigeminal nerve*, which conveys the blood from the lower part of the interpeduncular venous plexus to the superior petrosal or cavernous sinus

Whatever the direction of the basal vein, the venous rete on the surface of the tectum commonly discharges into an internal cerebral or the great cerebral vein rather than into the basal vein.

VENOUS DRAINAGE OF THE PONS The intrapontine arrangements of the venous system are similar to those of the arteries, but a certain amount of venous blood drains into the cerebellar tissues adjacent to the pons. Another difference consists in the smaller size and number of the central veins. This indicates that some of the blood which enters this region must be drained off by the lateral veins

The veins emerge from the pons in the same way as the arteries enter. The *central veins* fuse to form the *longitudinal vein of the pons*, which lies to one side or the other of the basilar artery. Sometimes there are two longitudinal venous trunks of the pons. Caudally, this system communicates with the anterior venous plexus of the medulla. Rostrally, it bifurcates and communicates either with the veins of the cerebellum or with one of the basal veins Some of the *lateral (or peripheral) pontine veins* communicate with the longitudinal vein of the pons, but many run laterally to join the anterior inferior cerebellar vein, which arises, where the brachium pontis pierces the cerebellum, as a result of the fusion of veins from the ventral surface of the cerebellum with those from the lateral side of the pons. The *anterior inferior cerebellar vein* often is connected by means of an anastomosing channel with the longitudinal vein of the pons, and it empties into the superior petrosal venous sinus.

VENOUS DRAINAGE OF THE MEDULLA. The venous drainage of the capillary network of the medulla is accomplished by vessels that follow a course which is the opposite of that of the arteries without being their satellites. The peripheral veins are fewer but larger than their corresponding arteries.

All the *medullary veins* drain into a complex,

subpial, venous rete, the loops of which are very small The elements of the venous net are freely connected along the dorsal and ventral midlines of the medulla by the *posterior and anterior median medullary veins,* respectively. The anterior median vein begins at the foramen cecum and communicates caudally with the corresponding channel on the cord It also communicates with a vein or venous plexus about the rootlets of the hypoglossal nerve (*hypoglossal vein* of Kadyi) This hypoglossal venous plexus drains into the hypoglossal canal. The posterior median vein originates rostrally from the choroid plexus of the fourth ventricle and passes backward to communicate with the corresponding channel of the cord It also communicates with channels which accompany the ninth and tenth nerves and which drain into the transverse venous sinus at the jugular foramen. Some of the blood from the posterior venous net drains rostrally into the plexus on the ventral surface of the cerebellum

VENOUS DRAINAGE OF THE SPINAL CORD The venous drainage of the cord is picked up from the capillary plexus by veins that run out of the cord in a location and manner corresponding to those in which the arteries enter These veins drain into a *peripheral venous plexus,* which exhibits three more or less distinct, longitudinal, stemlike channels upon both the ventral and dorsal aspects of the cord, the *anterior medullispinal veins* and the *posterior medullispinal veins,* respectively Of the anterior medullispinal veins, one lies along the ventral fissure and one along the line of emergence of the ventral roots of each side Of the posterior medullispinal veins, one lies along the posteromedian sulcus and one along each posterior lateral sulcus Those elements of the medullispinal system which correspond in position to arteries bear names similar to those of the arteries The system contains no valves except a few inefficient monocusps

The anterior medullispinal veins are rostrally continuous with a similar arrangement on the medulla Caudally, this system is elongated into a filament, the terminal venous filament or vein of the filum terminale, which drains into the vein of the dura mater The anterior medullispinal veins drain into ventral radicular veins which lie on the ventral surfaces of the ventral roots They are more numerous but smaller than the corresponding arteries

The posterior medullispinal veins are heavier than the anterior, and this system drains into several trunks which pass between the filaments of the dorsal root and unite on the ventral or, less frequently, on the dorsal surface of the root as the dorsal radicular vein. There are fewer dorsal radicular veins than arteries, but those which are present are larger. There are generally up to six prominent elements.

The *dorsal and ventral radicular veins* unite in a common vessel on the mixed nerve that is called the *lateral spinal vein.* This receives a venous offset from the dura mater and then anastomoses with the *internal vertebral venous plexuses,* of which there are two, a dorsal and ventral, both freely connected with each other by a cylindric anastomosis situated between the dura and the ligaments of the cord. Into them empty the basivertebral veins, one of which drains the body of each vertebra Through each intervertebral foramen, they also communicate extensively with the *external vertebral venous plexuses,* which lie external to the bones This brings them into communication with the veins of the thoracoabdominal cavities. In the cervical region, the internal venous plexuses communicate freely with the vertebral vein, which accompanies the vertebral artery through the foramina of the transverse processes of the upper six cervical vertebrae but does not enter the cranium. It arises from tributaries in the suboccipital triangle and empties into the internal jugular vein Since the internal venous plexuses anastomose with the veins of the dura about the base of the brain, an indirect connection exists between them and the vertebral vein. Ordinarily, the blood in this vertebral system flows vertebrifugally, but whenever intrathoracic or intra-abdominal pressure is increased, as it normally is during coughing or lifting weight, the direction of flow is reversed

ANASTOMOSIS AMONG VENOUS CHANNELS Throughout the cranium, the veins of the brain, of the meninges (the venous sinuses), of the skull bones themselves (the diploic veins), and of the various extracranial plexuses, anastomose freely. It is important to realize that, through the epidural and vertebral veins, it is possible for material to pass from a locus as distantly situated as the pelvis and arrive at the skull without ever traversing the caval, portal, or pulmonary circuits Once having reached the skull, such material can pass, by

a retrograde course, into the meningeal channels and, from them, into the brain. A reversal of venous flow is not unusual in any portion of the system and can occur under normal physiologic conditions of increased intrathoracic or intra-abdominal pressure.

The Jugular System. The venous drainage of the head and neck passes through the neck in either the jugular or the vertebral venous systems. The *jugular system*, the principal channel, is the only anteriorly situated route. The main vessel in the jugular system is the *internal jugular*, which begins just below the jugular foramen. The three compartments of the jugular foramen transmit (through the anterior compartment) the inferior petrosal sinus (through the intermediate compartment), the ninth, tenth, and eleventh cranial nerves, and (through the posterior compartment) the transverse sinus and some arterial offsets to the meninges. The *internal jugular vein* is formed by the union of the inferior petrosal and transverse sinuses. On its medial side, the internal jugular is joined, in succession, by the pharyngeal, lingual, facial, superior thyroid, and middle thyroid veins On the lateral side, it is accompanied by the external jugular vein (old term, dorsal external or superficial jugular), which communicates with it by means of one or two variable oblique jugular veins. The *external jugular* begins as the confluence of the posterior auricular and retromandibular or facial veins and empties into the subclavian The union of the subclavian and internal jugular constitutes the *brachiocephalic vein*. The *anterior jugular vein* (old term, ventral external or superficial jugular) (Fig 1-107B) begins in the submental area and proceeds down the front of the neck just to the side of the midline. At the sternal notch, the two anterior jugular veins are interconnected by means of an anastomotic channel called the jugular venous arch.

VERTEBRAL VENOUS SYSTEM The vertebral column encloses a longitudinal venous plexus, the internal vertebral venous plexus, which lies between the bone and dura, and is in turn encompassed by the external vertebral venous plexus. Both these plexuses consist of anterior and posterior parts. The *external vertebral venous plexus* is much better organized in the cervical regions than elsewhere.

The *internal vertebral venous plexus* receives tributaries from both the spinal cord and the osseous structure of the vertebrae. At the foramen magnum, it communicates with the basilar plexus, the occipital sinus, and vertebral veins In its course through the cervical vertebrae, it is freely connected, by intervertebral veins, with the external vertebral venous plexus throughout

The *external vertebral venous plexus* anastomoses freely with the vertebral vein in the cervical region, and with the intercostal, lumbar, and lateral sacral veins below. As noted, in discussing anastomoses among venous channels, the vertebral venous plexuses provide a route by means of which material can progress longitudinally along the outside as well as the inside of the vertebral column.

The *vertebral vein* originates in a congeries of vessels about the transverse process of the first cervical vertebra. Among these vessels, some come from the suboccipital muscles and vertebral venous plexuses. The upper end of the vertebral vein anastomoses with the occipital and internal jugular. It forms a plexiform arrangement about the vertebral artery and accompanies it through the foramina in the transverse processes of the cervical vertebrae. After passing downward and receiving additional offsets from the vertebral venous plexus, it emerges from below the sixth or, sometimes, seventh cervical vertebra, and ends in the brachiocephalic vein.

The *anterior vertebral vein* (old term, ascending cervical) lies on the anterior surface of the transverse processes of the cervical vertebrae and accompanies the vertebral vein in its downward course to enter it near its entrance into the subclavian.

DYNAMIC CHANGES IN CEREBRAL CIRCULATION[3]

Influence of Blood Gases. The amount of blood that flows through the brain is influenced by changes in the diameter of the cerebral arteries, and this is primarily controlled by the carbon dioxide and oxygen concentrations in the blood circulating through them High carbon dioxide concentration results in marked vasodilatation, low oxygen level has a similar but lesser effect Unless the systemic blood pressure falls below 70 mm Hg, changes in general blood pressure have no notable effect upon cerebral blood flow

Influence of Vasomotor Nerves. Although the blood vessels are provided with many perivas-

[3] See also Part 2, Chap 24 *Editor*

cular nerves, which can be found even on arterioles as small as 30 μ, there is no evidence that total cerebral flow is notably influenced by neurogenic constriction or dilatation. Many of the nerves found on the vessels are sensory. The remainder are autonomic and are derived from the cervical sympathetic chain or the facial nerve. The *sympathetic fibers* exert a weakly constrictor effect and enter the cranial fossae over the internal carotid and vertebral plexuses The *parasympathetic vasodilator fibers* travel over the greater petrosal nerve to the internal carotid plexus

The various autonomic nerves seem to be part of a mechanism for only local changes in blood flow and do not appear to be integrated into a mechanism for regulation of the over-all flow through the brain as a whole

Resilience in Cerebrovascular Tone. According to the *Munro-Kellie doctrine*, the cerebrospinal canal is a closed space and its contents are incompressible Such a statement is incomplete in failing to take into consideration that the volume of the closed system is itself variable, because it is partly ligamentous. Moreover, the Munro-Kellie doctrine cannot be taken to imply that nothing can enter the cerebrospinal canal for it *is obvious that* blood does Variation in the volume of contents within the cranial case must therefore be possible, and obviously blood is phasically entering and leaving the space, so that there is a degree of variation in the volume of the various individual contents of the space Moreover, pressure within the space can and does change, and this is a reflection of changing volume The volume of the arterial bed changes, not only with the constant alterations of pulsation, but also because of periodic passive dilatation against the normal elasticity of healthy muscle fibers, which are themselves susceptible to physical as well as chemical stimulation As long as normal vascular tone is operative, it would seem, therefore, that no large exercise of neural influence is required to provide for the regulation of an even flow of blood through the brain as a whole. The physical and chemical characteristics of the blood, constantly conditioned in time by factors such as the partial pressure of gases and attenuation of pressure according to Poiseuille's law, are such that, acting against a resilient muscular bed, nothing more than minor local assistance to constriction is required to maintain adequate cerebral flow

Local Effects of Physical and Chemical Stimuli. It has been stated that the vessels are sensitive to physical stimuli; this is particularly true of the large vessels of the neck and at the base of the brain, where even the petrous part of the internal carotid can be seen to constrict to an astonishing degree during surgical procedures. A local chemical vasodilator effect has been postulated by Chapman et al, who have applied the name *neurokinin* to a polypeptide substance which they feel they demonstrated as a result of the activity of vasodilator nerves. This material is said to be similar to bradykinin, but distinct from it, and also to be detectable in the spinal fluid of patients with certain generalized neurologic disorders

Changes in Cerebrospinal Fluid Pressure. Increasing cerebrospinal fluid pressure results in an increase in resistance to blood flow through the brain This is offset by a rise in systemic blood pressure until it becomes impossible for the heart to maintain circulation through the capillary bed of the medulla. At this point, cerebral circulation fails, but up to this point there is no impairment in neural function (Brogden et al). Thus, the failure of the function of the neural system is not a gradual process but occurs precipitously. It is of interest that if the intracranial (cerebrospinal) fluid pressure is suddenly released in such a situation, resistance to blood flow through the brain is not immediately reduced. It is believed that this might be because of the development of spasm in the blood vessels which have been subjected to a sudden head of pressure Vasospasm may also be the consequence of the intra-arterial injection of an irritating chemical substance, as may occur during angiography

Patients with recent osseous defects in the skull are unusually sensitive to the effects of postural hypotension, and this has been correlated with a loss in the protective potential of the rigid container of the brain The physical advantage of the rigidity of the cranium in assuming the upright posture must be very small, and such an explanation of the observed phenomenon appears gratuitous to the writer. In general, this phenomenon is seen only in patients who are suffering from the acute effects of trauma or who have been in bed for a long time, it would therefore not seem to be necessarily related to the possible loss of a protective negative extravascular pressure.

I

The bronchial and esophageal arteries

BARRY J. ANSON

The arteries of supply to the bronchi and the esophagus form an uninterrupted series, which, in its entirety, involves anatomic regions from cervical to abdominal levels. Of the two sets, the arteries to the esophagus are topographically more inclusive, since the most cranially situated source is the inferior thyroid, and the most caudally placed vessel of origin is the hepatic division of the celiac artery

Although interrelationship of arteries is important surgically, to make this presentation easier for the reader to follow it will be given not according to interrelationships but in two sections, with the description of the bronchial arteries preceding that of the esophageal arteries.

BRONCHIAL ARTERIES

Origin. The bronchial arteries, with but few exceptions, take origin from the proximal part of the thoracic aorta (Figs. 1-113 and 1-114). They may arise independently, in multiples from a common stem of aortic derivation, or in company with a functionally unrelated vessel. In fact, so common is departure from an archtypical plan, that 9 distinct types of origin were encountered in 300 specimens (Fig. 1-115). The most commonly encountered pattern (type I in Fig 1-115, 47 67 per cent) is that described as "normal" in standard textbooks. In such instances, 2 left bronchial arteries and 1 right are present In every case, there is at least 1 bronchial artery to each lung, and this simplest vascular arrangement occurs next in the order of frequency as type II (24 33 per cent) The third major group, type III, is characterized by bilateral duplication of the arteries (14 33 per cent of cases).

In 14 cases (type IV; 7 67 per cent) the pattern is the reverse of that in type I, with 1 artery to the left and 2 to the right lung. The arteries to the left lung are increased to 3, with a single vessel persisting on the right side, in 6 cases (type V; 3.0 per cent). A maximum number of 5 arteries occurred in a few instances, either 3 on the left and 2 on the right (type VI, 1 67 per cent) or in the reverse of this scheme (type VII, 0 67 per cent). The remaining examples have 4 arteries to 1 lung, and a solitary vessel to the opposite organ The quadruple pattern is found on the left in type VIII (0.33 per cent), on the right, in type IX (0 33 per cent).

On the basis of sides, two-thirds of all right lungs are supplied by a single bronchial artery (100, 67.7 per cent), whereas about one-third of left lungs are so supplied (47, 31.8 per cent) On the other hand, 62 per cent of all left lungs are provided with 2 bronchial arteries, while half that number (32 per cent) of right lungs have duplicated vessels. Three arteries to the left lung are observed in 9 bodies (6 per cent), and to the right lung in but 1 instance (0 67 per cent) Four arteries supply a right and a left lung in separate cases

Classification of bronchial arteries into types on the basis of pattern frequency may be supplemented by a consideration of the manner of origin of the vessels represented

Type I. Two left, 1 right (61 cases, 40 67 per cent)

A Each arises separately (58, 38 7 per cent)

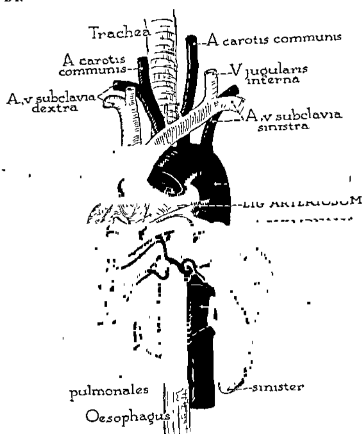


Fig 1-113. Bronchial arteries and related structures (shown in dissection of the posterior mediastinum). Within the thoracic cavity, the following structures have been removed pleura; heart and pericardium, inferior vena cava and azygos veins; both lungs except in their hilar portions

The bronchial arteries arise by a common stem, one division passing to each bronchus. The right bronchial vessel crosses anterior to the esophagus, to ramify on the anterior and inferior surfaces of the corresponding bronchus The vessel of the left side courses almost directly forward, attaining the inferior margin of the left bronchus; rami then pass to the anterior surface (From *Cauldwell et al*, 1948)

B Superior left and single right from common stem (1, 0 6 per cent)

C Inferior left and single right from common stem (1, 0 6 per cent)

D All 3 from common stem (1, 0 6 per cent)

Type II One left, 1 right (32 cases, 21 33 per cent)

A. Each arises separately (28, 18.7 per cent)

B Both from common stem (4, 2 7 per cent)

Type III Two left, 2 right (31 cases, 20 67 per cent)

A Each arises separately (9, 6 per cent)

B Inferior left and inferior right from common stem (9, 6 per cent)

C. Superior left and inferior right from common stem (8, 5 3 per cent)

D. Two common stems (2, 1.2 per cent)

E. Superior left and superior right from common stem (2, 1 2 per cent)

F. Two left and inferior right from common stem (1; 0 6 per cent)

Type IV. One left, 2 right (14 cases, 9 33 per cent)

A. Each arises separately (9, 6 per cent)

B Single left and inferior right from common stem (5, 3 33 per cent)

Type V Three left, 1 right (6 cases, 4 per cent)

A Each arises separately (3, 2 per cent)

B. Superior and middle left, single

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The arteries of supply to the bronchi and the esophagus form an uninterrupted series, which, in its entirety, involves anatomic regions from cervical to abdominal levels Of the two sets, the arteries to the esophagus are topographically more inclusive, since the most cranially situated source is the inferior thyroid, and the most caudally placed vessel of origin is the hepatic division of the celiac artery

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BRONCHIAL ARTERIES

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Classification of bronchial arteries into types on the basis of pattern frequency may be supplemented by a consideration of the manner of origin of the vessels represented

Type I. Two left, 1 right (61 cases; 40 67 per cent)

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ture and, incidentally, to indicate the discrepancies that may arise from the designation of posterior intercostal arteries as reference sites, the following data on the right intercostobronchial arteries may be of service.

One right intercostobronchial artery (or more) occurs in 133 cadavers (88.7 per cent). A right bronchial artery is associated with a single intercostal artery in 129 cases (86 per cent). In 4 cases (2.7 per cent), each of 2 right bronchial arteries arises in common with an intercostal artery: in 3, in common with the first and second aortic intercostal arteries; and in 1, with the first and third. In 17 cases (11.3 per cent), the right bronchial arteries are in no way associated with intercostal

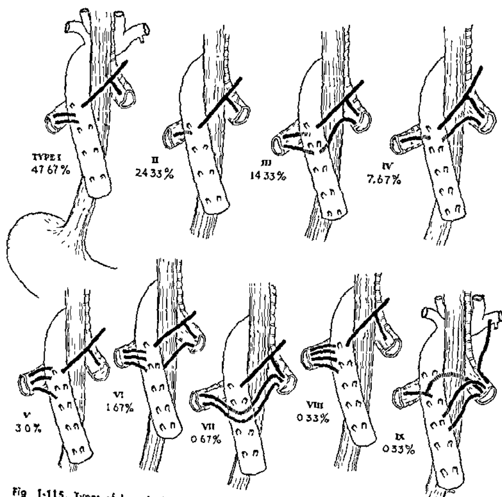


Fig. 1-115. Types of bronchial arterial supply; from a study of 300 specimens. Schematically shown, as if viewed from the dorsal aspect. The classification is based on the origin, number, and course of the vessels. I, Pattern of bronchial arterial supply most commonly encountered in the authors' laboratory, and described as typical or normal in standard textbooks: two left and one right bronchial artery. II, A type next in order of frequency in which a single artery passes to each bronchus. III, An arrangement third in the order of frequency, in which a pair of arteries supplies each bronchus. IV, First in the series of remaining types (together, approximately 15 per cent of 300 specimens), in which the arrangement occurring in type I is reversed. V, Differing from type I in that three arteries (rather than two) are present on the left. VI, Differing from the preceding type in the occurrence of two arteries (rather than one) for the right bronchus. VII, The reverse of type VI, there being two bronchial arteries on the left, three on the right. VIII, An infrequent arrangement of arteries supplied to the bronchi, in which four pass to the left, only one to the right. IX, An equally infrequent pattern of supply, in which the arrangement is the reverse of that in the preceding type (VIII). (From Swigart et al., 1950, and Cauldwell et al., 1948.)

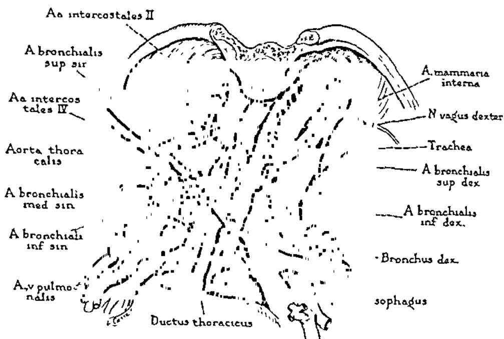


Fig. 1-114. Bronchial arteries and related structures in the posterior mediastinum, seen from behind. The transected thoracic aorta has been reflected and the azygos vein excised, in order to demonstrate course and termination of bronchial arteries, which are in series with the aortic intercostal arteries (From *Cauldwell et al.*, 1948.)

right from common stem (2, 1 3 per cent)

C Inferior left and single right from common stem (1, 0.67 *per cent*)

Type VI Three left, 2 right (3 cases, 2 per cent)

A. Each arises separately (1, 0 67 per cent)

B. Superior left and inferior right from common stem (1, 0 67 per cent)

C. Inferior left and right from common stem (1, 0 67 per cent)

Type VII Two left, 3 right (1 case, 0 67 per cent) Two common stems superior left and middle right, inferior left and right

Type VIII Four left, 1 right (1 case, 0 67 per cent), each arising separately

Type IX. One left, 4 right (1 case, 0 67 per cent) Superior right from right subclavian, single left and second right from common stem, third and fourth right arising separately

The bronchial arteries to the right lung differ markedly from those to the left in respect to sites of origin from the aorta Those to the right side arise from the corresponding lateral or dorsolateral aspect of the aorta, in the former position when separate, and in the latter position separately or in combination with an intercostal artery. When this last arrangement occurs, the point of origin is in longitudinal alignment with the other intercostal arteries (Fig. 1-113). In cases with single right arteries, this pattern occurs consistently. On the contrary, this arrangement does not occur regularly in cases with multiple right vessels, in specimens of the latter type, the superior bronchial artery is likely to arise in common with an intercostal artery, whereas the inferior bronchial artery originates from the anterior surface of the aorta In no case does a right bronchial artery arise from the left side of the aorta

A *right bronchial artery* frequently arises in common with an intercostal artery The term *intercostobronchial* is hereinafter applied to these vessels, in order to obviate artificial and confusing distinction between parent stem and branch, in the majority of cases, little difference in size is observed between the components of the bifurcated vessel.

That the right bronchial artery frequently arises in common with an intercostal artery has long been known However, confusion has resulted from failure to indicate accurately the intercostal vessels associated with this pattern. Many authors of textbooks classify the segmental arteries on the basis of the intercostal spaces supplied (posterior intercostal arteries), others identify them more satisfactorily on the basis of their relative position as aortic derivatives (aortic intercostal arteries). Toward an accumulation of needed information of accurate na-

from the anterosuperior surface of the arch immediately caudad to the roots of the brachiocephalic and left common carotid arteries, and courses anterior to the trachea to reach the corresponding bronchus In the 21 remaining cases, the artery arises from some portion of the concavity of the arch cranial to the level of the first intercostal vessels In 15 (10 per cent) of these cases, a single vessel passes to the left bronchus, in 4 (2.7 per cent), a common stem provides arteries to right and left bronchi, and in 2 specimens (1 3 per cent), a single right bronchial artery occurs In a single specimen the entire bronchial arterial supply derived solely from the aortic arch (cranial to the highest aortic intercostal artery) 1 of the 4 specimens (see above) with a common stem for both lungs arising from the concavity of the arch contributes 1 right and 2 left bronchial arteries to corresponding bronchi

In 3 instances (2 per cent), anomalous bronchial arteries are found to arise from a subclavian trunk. In 1 of these, the aberrant vessel takes origin from the right subclavian artery and passes to the right superior lobar bronchus (Fig 1-115, type IX); in the second, origin is through a common stem which, derived from the base of the left subclavian artery anteromedial to the internal thoracic artery, provides branches to right and left superior lobar bronchi, in the third case, a single artery arises from the left subclavian artery and passes to the corresponding superior lobar bronchus. In each instance the arteries of subclavian origin are supplementary to 1 (or more) bronchial artery of aortic origin In the series described herein, no specimen occurs in which major bronchial arteries are derived from the costocervical trunk, inferior thyroid artery, or internal thoracic artery, although small anastomotic twigs between these vessels are frequently encountered

[illegible]

moses between the bronchial and aortic esophageal branches are regularly present, in 31.3 per cent of cases, major anastomoses occur between inferior bronchial and esophageal arteries. Right bronchial arteries from intercostobronchial trunks always supply the dorsal aspect of the distal portion of the trachea and the adjacent segment of esophagus. Right inferior aortic arteries supply the esophagus liberally, as would be expected from the dorsal transesophageal course of the vessel

One (or more) constant large esophageal artery arises from the anterior aspect of the thoracic aorta opposite vertebrae T8 to T10 In 3 cases, primary aortic esophageal arteries contribute branches of the caliber of bronchial arteries to the lower lobe of the lung (left, 2; right, 1), entering the parenchyma through the pulmonary ligament in its middle and inferior thirds

In approximately 10 per cent of cadavers, large pericardial arteries are derived from the bronchial arteries. These are more frequently associated with a right bronchial artery that passes superior to the left main bronchus, and with right inferior bronchial arteries

The paratracheal and bronchial lymph nodes receive an abundant supply from the bronchial arteries. Often the artery traverses a node en route to the bronchus. Although in the current series no major bronchial artery is observed to rise directly from an internal thoracic artery, anastomoses effected by small twigs occur constantly between the superior right bronchial and the corresponding internal thoracic arteries These twigs extend either longitudinally or obliquely dorsad to the superior vena cava and lateral margin of the trachea.

Anastomosis is effected between superior bronchial arteries and the right subclavian and superior intercostal arteries, the minute rami derived from the network of vessels then supplying paratracheal and proximal bronchial lymph nodes

Indirect anastomosis between the right bronchial artery of intercostobronchial derivation and the superior intercostal and subclavian arteries is also established through the first aortic [illegible]

[illegible] gins of bronchial *arteries range from the third* to the eighth thoracic vertebral levels, nearly half the arteries (right, 48 4 per cent; left, 46 9 per cent) are related to the sixth segment, and one-third (right, 34.4 per cent, left, 33 per cent) to the fifth segment (see Tables 1-2 and 1-3, in which the vertebral levels are tabulated by cases and by arteries, respectively). The remainder arise above and below the vertebral area just described, with the greater degree of variation depending upon the total number of bronchial arteries in any particular specimen.

Considering bronchial arteries of aortic origin in relation to vertebral bodies, the following observations may be presented. origin opposite a single vertebral level in 57 cases (38 per cent), opposite 2 adjacent levels in 85 cases (56 67 per cent); opposite 3 adjacent levels in only 8 specimens (5 3

arteries; they arise from the aorta or subclavian artery, either separately or in company with other right or left bronchial vessels.

Of an over-all total of 205 right bronchial arteries (to 150 right lungs), 137 (66.8 per cent) in 133 cases are components of intercostobronchial trunks. The remaining 68 vessels (33.2 per cent), occurring in 60 cases, are unrelated to the intercostal vessels.

The right bronchial and first aortic intercostal arteries are derived from a common stem in 117 cases. This represents 78 per cent of total cases (150) or 88 per cent of those (133) demonstrating intercostobronchial relationship. The first aortic intercostal artery in these 117 cases supplies intercostal spaces from 1st to 4th, as solitary or combined trunks. In 82 (of 117) cadavers, a single intercostal space is vascularized, the 3d being the space most commonly supplied in this manner. In 31 (of 117) cases, an intercostal artery bifurcates distad to its emergence from an intercostobronchial stem to supply 2 adjacent interspaces, the 2d and 3d spaces being those most frequently cared for in this manner. In only 4 cases (of 117) are 3 adjacent interspaces supplied by a single derivative of an intercostobronchial artery.

The second aortic intercostal artery is associated with a right bronchial artery in 11 cases (7.33 per cent of 150, 8.25 per cent of 133). The second aortic intercostal artery supplies the intercostal spaces from 3 to 5, and the 4th space is also frequently supplied by this segmental artery. Only 1 of the 11 combined intercostal vessels supplies more than 1 interspace.

A third aortic intercostal artery is in bronchial combination in 2 instances (1.33 per cent of 150, 1.5 per cent of 133). In 1 case a single right bronchial artery is involved, in the second, an inferior right bronchial artery arises with the third aortic intercostal artery, while the corresponding superior bronchial artery duplicates the relationship with the first aortic intercostal artery.

In 4 cases (2.67 per cent of 150, 3 per cent of 133), two intercostobronchial arteries occur: the first and second aortic intercostal in 3 instances, the first and third in 1 specimen.

The *left bronchial arteries* usually take origin from the anterior surface of the thoracic aorta or from the concavity of the aortic arch. They may also arise from the right side of the aorta, usually in common with a right bronchial artery, but they will arise rarely from the left side.

Unlike the right bronchial arteries, those to the left lung seldom arise in common with an intercostal artery. When this association is found, a right, rather than a left, intercostal artery is involved (a rare case of situs inversus viscerum being exceptional).

In 6 cadavers (4 per cent), 1 left bronchial artery (or more) arises in common with a right intercostal artery. These exhibit the following features: (1) a common trunk for a superior left bronchial, middle right bronchial, and second aortic intercostal artery; (2) a common trunk for a single left bronchial, single right bronchial, and first aortic intercostal artery, (3) a common trunk or superior and middle left bronchial arteries, a single right bronchial artery, a second aortic intercostal artery, and a second common trunk providing for the left inferior bronchial and third aortic intercostal artery; (4) left superior bronchial and first aortic intercostal artery; (5) a single left bronchial and first aortic intercostal artery; and (6) a single left bronchial and third aortic intercostal artery. In an over-all total of 267 bronchial arteries to 150 left lungs, 8 arteries (3 per cent) in the above-described cases arise with right aortic intercostal arteries: 3 each with the first and second, 2 with the third intercostal artery. Four of the 8 are unassociated with a right bronchial artery arising from the same stem.

In three-fourths of the cadavers (111; 74 per cent), all bronchial arteries arise independently of each other from the aorta or subclavian artery. In the remaining cases (39, 26 per cent), 2 or more bronchial arteries arise from common stems in the following general patterns: (1) 1 right and 1 left bronchial artery in 34 cases (22.6 per cent), (2) 2 left and 1 right in 3 cases (2 per cent); and 2 common trunks, from each of which arise a right and left artery, in 2 cases (1.3 per cent). In specimens with a common trunk for 1 right and 1 left artery, the inferior vessels more frequently occur together (11 cases, 7.3 per cent); and somewhat less frequent is the association of a superior left and inferior right vessel (9 cases, 6 per cent). It is of interest that the right bronchial artery usually participates in the formation of a common stem with a left when the former vessels are multiple. Right-sided multiplicity of arteries occurs in 50 cases (33.3 per cent), the right artery is part of a common trunk with the left in 39 cases (26 per cent), but in only 8 (5.33 per cent) of these is the associated right artery solitary to the right lung. In 3 cases (2 per cent) a common stem is the immediate source of 3 bronchial arteries: 2 left and a single right, in 2 instances, 2 left and an inferior right in the third case. In the 50 cases of multiplicity of right bronchial arteries, 42 (27.3 per cent) have both intercostobronchial and aortic sites of origin.

In 22 cadavers (14.7 per cent), 1 (or more) bronchial artery arises from the arch of the aorta. In a single instance a left bronchial artery emerges

from the anterosuperior surface of the arch immediately caudad to the roots of the brachiocephalic and left common carotid arteries, and courses anterior to the trachea to reach the corresponding bronchus In the 21 remaining cases, the artery arises from some portion of the concavity of the arch cranial to the level of the first intercostal vessels In 15 (10 per cent) of these cases, a single vessel passes to the left bronchus, in 4 (2 7 per cent), a common stem provides arteries to right and left bronchi, and in 2 specimens (1.3 per cent), a single right bronchial artery occurs. In a single specimen the entire bronchial arterial supply derived solely from the aortic arch (cranial to the highest aortic intercostal artery). 1 of the 4 specimens (see above) with a common stem for both lungs arising from the concavity of the arch contributes 1 right and 2 left bronchial arteries to corresponding bronchi.

In 3 instances (2 per cent), anomalous bronchial arteries are found to arise from a subclavian trunk In 1 of these, the aberrant vessel takes origin from the right subclavian artery and passes to the right superior lobar bronchus (Fig 1-115, type IX), in the second, origin is through a common stem which, derived from the base of the left subclavian artery anteromedial to the internal thoracic artery, provides branches to right and left superior lobar bronchi, in the third case, a single artery arises from the left subclavian artery and passes to the corresponding superior lobar bronchus. In each instance the arteries of subclavian origin are supplementary to 1 (or more) bronchial artery of aortic origin In the series described herein, no specimen occurs in which major bronchial arteries are derived from the costocervical trunk, inferior thyroid artery, or internal thoracic artery, although small anastomotic twigs between these vessels are frequently encountered

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In the author's series, the predominant blood supply of the middle third of the esophagus is derived from the bronchial arteries. Anastomoses between the bronchial and aortic esophageal branches are regularly present, in 31 3 per cent of cases, major anastomoses occur between inferior bronchial and esophageal arteries. Right bronchial arteries from intercostobronchial trunks always supply the dorsal aspect of the distal portion of the trachea and the adjacent segment of esophagus. Right inferior aortic arteries supply the esophagus liberally, as would be expected from the dorsal transesophageal course of the vessel

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Considering bronchial arteries of aortic origin in relation to vertebral bodies, the following observations may be presented origin opposite a single vertebral level in 57 cases (38 per cent), opposite 2 adjacent levels in 85 cases (56 67 per cent); opposite 3 adjacent levels in only 8 specimens (5 3

per cent). In 55 cases (36.7 per cent) the left bronchial arteries arise opposite T5 and T6 as a unit, in 26 cases (17.3 per cent) opposite T6 alone. Thus, in 106 of 150 bodies (70.1 per cent), all left bronchial arteries of aortic origin emerge from a segment limited by the cranial margin of T5 and the caudal margin of T6.

The topographic relations on the right side are somewhat different, because of the association of the bronchial with intercostal arteries. In 57 cases (38 per cent) in which the bronchial arteries are not associated with intercostal arteries, the right bronchial arteries arise opposite single vertebral levels. T6, in 26 cases (17.3 per cent), T5, in 18 cases (12 per cent); T7, in 4 cases (2.7 per cent); and T4, in 3 cases (2 per cent). Right bronchial arteries unassociated with intercostal arteries arise from the aorta at a slightly lower level than those on the left side. This circumstance is owing, in part, to the occurrence of the intercostobronchial trunk on the right, which generally arises at the same level as the left superior bronchial artery

On the basis of vertebral level of origin considered by arteries, 260 left bronchial vessels (of an over-all total of 267) arise from the descending aorta or from the aortic arch (Table 1-3) Almost half the left arteries emerge from the aorta opposite the sixth thoracic vertebral level The range of origins extends between extremes of T3 and T8, with the majority of left bronchial arteries (80 per cent) arising opposite the combined levels of T5 and T6

In the 57 cases in which the right bronchial arteries arise from the aorta independent of intercostal arteries, there is a total of 64 vessels, the remaining 141 arteries (in 93 cases) take origin in common with intercostal arteries or are derived from the subclavian artery (2 cases, 2 vessels) As with the left side, approximately half (31 of 64 arteries, or 48.4 per cent) of the independent right bronchial arteries arise from the aorta opposite T6, and 82 8 per cent opposite the combined levels of T5 and T6. The range, however, is more restricted than on the left side, extending between T4 and T7. Thus, 8 out of 10 right and left independent aortic bronchial arteries originate opposite the bodies of the fifth and sixth thoracic vertebrae

Course. The right bronchial artery is more constant than the left in respect to origin, course, and distribution A single right artery arises from the corresponding lateral aspect of the aorta, or from its dorsolateral surface when in combination with an intercostal artery In the latter type (88 67 per cent), the artery courses cranialward to pass between the azygos vein and the vertebral bodies At or near this site, the intercostobronchial artery bifurcates to provide an aortic intercostal artery to the appropriate intercostal space and a definitive bronchial artery, the latter vessel leaving the parent stem at a variable angle to course obliquely caudalward and anteriorly, beneath the arch of the azygos vein, on the way to the right bronchus. The right bronchial artery is more frequently associated with the highest aortic intercostal artery; when it is not, the artery arises at too low a level to permit passage beneath the azygos arch. In a specimen with two right bronchial arteries, each of which arises in common with an intercostal artery, the right superior artery passes beneath the arch, the inferior one does not (Cauldwell et al, 1948) Since the artery lies in close relationship to the trachea and esophagus, it provides numerous twigs of supply to each.

When a right bronchial artery arises from the aorta unassociated with an intercostal artery, its course to the bronchus is usually more direct. From its origin on the anterolateral, lateral, or posterolateral aspect of the aorta, the artery passes anteriorly and cranialward, or anteriorly and lateralward, to the right of the esophagus to reach the bronchus Its relationship to the bronchus is similar to that of the branch derived from an intercostobronchial trunk, although it is generally found in a more caudal position on the posterior surface of the bronchus

An inferior right bronchial artery (present in 33 3 per cent of cases) arises either from the corresponding lateral or anterior surface of the thoracic aorta It may course to the right of and dorsal to, or to the left of and anterior to, the esophagus on its way to the right inferior lower bronchus (hyparterial bronchus of Aeby) Vessels of anterior origin may course superiorly to loop about the cranial aspect of the left main bronchus, and then pass inferiorly, inclining toward the right, on the anterior surface of the tracheal bifurcation, branches are supplied to adjacent lymph nodes en route, and the artery continues along the caudal border of the right main bronchus

In 11 33 per cent of the bodies (17 of 150), 1 right bronchial artery (or more) winds to the left and passes anterior to the esophagus on its way to the right main bronchus, in 13 of the cases, the right bronchial artery is derived from a common stem with a left bronchial artery, and in 4 cases the right bronchial artery arises separately from the aorta In 8 7 per cent of bodies (13 of 150), a right bronchial artery passes anterior to the trachea or the tracheal bifurcation to reach the

right main bronchus, in 8 of the cases the right bronchial artery arises in common with a left bronchial artery, and in 5 cases it has an independent aortic origin. One right bronchial artery, from a common stem, passes through the tracheal crotch to the anterior surface of the right bronchus, another, of independent aortic origin, passes anterior to the left main bronchus and bifurcation, then turns posteriorly through the crotch to reach the dorsal aspect of the right main bronchus.

In 39 cases (26 per cent), in which 1 (or more) left bronchial artery arises in common with a right bronchial, 21 (14 per cent) possess a common stem which courses to the left dorsal to the esophagus, and bifurcates at its lateral margin. The left bronchial artery then continues directly to the left main bronchus while the right artery passes anterior to the esophagus, or ascends to loop over the left bronchus and courses on the anterior aspect of the tracheal bifurcation.

In the case having 4 right bronchial arteries (Fig. 1-115, type IX), a strikingly anomalous *vessel arises* from the right subclavian artery immediately proximal to the origin of the corresponding internal thoracic artery. It descends to the right of the trachea and dorsal to the superior vena cava, after crossing anterior to the azygos vein, it enters the pulmonary hilum along the cranial border of the superior lobar bronchus.

The bronchial arteries to the left lung follow a more direct and simpler course. Since most of them arise from the anterior surface of the aorta immediately behind the left main bronchus, they must pass anteriorly to reach the bronchus. In approximately one-third of cases (34.7 per cent), 1 (or more) left bronchial artery arises from the right anterolateral or lateral aspect of the aorta, and passes dorsal to the esophagus to reach the left bronchus. In the single instance in which the left bronchial artery courses *anterior to* the esophagus, it is a derivative of a common stem with a right bronchial artery. In another case, a left bronchial artery emerges from the right dorsolateral aspect of the aorta at the level of the second right aortic intercostal artery, and winds ventral to the aorta to reach the left bronchus. A left bronchial artery passes anterior to the trachea, proximal to the bifurcation, in 3 cases (2 per cent), and its *anterior* course is restricted to that aspect of the left bronchus alone in 8 specimens (5.33 per cent). In 2 instances of the latter pattern, both superior and inferior left bronchial arteries have a similar course, providing a total of 10 arteries so located (2.67 per cent of total left arteries).

Anastomotic vessels of dissectible size are found connecting adjacent left bronchial arteries in 4 cases (2.67 per cent): (1) between superior and inferior bronchial arteries; (2) between superior and middle bronchial arteries; (3) between middle and inferior bronchial arteries, and (4) between the superior and second of 4 arteries. These anastomoses extend either obliquely or vertically across the posterior aspect of the main bronchus. In 3 cases (2 per cent), a major anastomosis extends in transverse plane to connect a right and left bronchial artery; and in 1 of these the anastomotic channel courses anterior to the esophagus. Major anastomoses between inferior bronchial and primary aortic esophageal arteries are found in 47 cases (31.3 per cent), but small anastomoses between these two classes of vessels occur in every case studied.

In 8 cases (5.33 per cent), arteries to the inferior lobar bronchi arise craniad to the origins of superior lobar supply; in 5 of these the artery courses to the right lung; in 1, to the left, and in 2, a common stem bifurcates to supply both lungs.

Contrary to accepted opinion, the definitive bronchial artery seldom occupies the midportion of the dorsal membrane of the main bronchus. The superior bronchial arteries usually pass cranialward to reach the main bronchi (on the right side, at the site of bifurcation, on the left side, approximately 1 cm distad to the *bifurcation*). The artery then tends to follow the posterosuperior margin of the cartilaginous part of the bronchus, at the site of attachment to the dorsal membrane, to the superior lobar bronchus. Less frequently the entire course is along the anterior *surface of* the bronchus. Prominent twigs are often sent to the anterior aspect of the bronchus, even when the main vessel is more dorsally placed.

The *inferior* bronchial arteries tend to pursue a transverse course across the pericardium in the interval caudad to the tracheal bifurcation on their way to the posterosuperior or posteroinferior aspect of the inferior lobar bronchus. In their course, *the* arteries provide descending anastomotic rami to the esophagus and to posterior mediastinal tissue. In many cases, the artery follows the most dependent surface of the bronchus. *Arterial* rami to the anterior aspect of the inferior lobar bronchus are seen

less frequently than are those of superior bronchial origin to the corresponding bronchus.

TABLE 1-2. VERTEBRAL LEVEL OF ORIGIN OF BRONCHIAL ARTERIES IN 150 CASES

Origin	Left		Right	
	Cases	*Per cent*	*Cases*	*Per cent*
Arch of aorta	20	13 3	6	4.0
T3	1	0.7	0	0 0
T4	13	8.7	5	3 3
T5	5	3 3	1	0.7
T6	1	0 7	0	0.0
Subclavian artery	2	1 3	2	1.3
Left	2	1 3	1	0 7
Right	0	0 0	1	0 7
Descending aorta	150	100 0	57	38 0
T4	4	2.7	3	2.0
T4 and 5	8	5 3	2	1 3
T4 and 6	3	2 0	0	0 0
T5	26	17 3	18	12 0
T5 and 6	55	36 7	4	2 7
T5, 6, and 7	5	3 3	0	0 0
T5 and 7	1	0 7	0	0 0
T6	25	16 7	26	17.3
T6 and 7	18	12 0	0	0 0
T6, 7, and 8	3	2 0	0	0 0
T7	2	1 3	4	2 7

TABLE 1-3 VERTEBRAL LEVEL OF AORTIC ORIGIN BY ARTERY

Level of origin	Left		Right	
	Number	*Per cent*	*Number*	*Per cent*
T3	1	0 4	0	
T4	24	9 2	7	10 9
T5	86	33 1	22	34 4
T6	122	46 9	31	48 4
T7	26	10 0	4	6 3
T8	1	0 4	0	
Total	260	100 0	64	100 0

Terminally, in the region of the hilum, the single right bronchial artery bifurcates to supply superior and inferior lobar bronchi and their secondary subdivisions by multiple branches. In the presence of multiple arteries, the superior bronchial artery follows the cranial border of the superior lobar bronchus, while the inferior bronchial artery courses along the caudal, or posteroinferior, border of the inferior lobar bronchus; a middle bronchial artery, when present, tends to subdivide at the main bronchial bifurcation and to send rami to both superior and inferior lobar bronchi Immediately distad to the bifurcation of the main bronchus, each arterial ramus usually assumes a more central position on the posterior membranous wall. Peribronchial arborization and anastomoses are common in the region of the hilum.

ESOPHAGEAL ARTERIES

The esophagus receives arteries throughout its course, from the inferior thyroid in the neck to the branches of the celiac in the abdomen The arteries will be discussed in the order of source, from the thyroid level above to the gastric level below.

Cervical Portion of the Esophagus. The arteries sent to this portion of the esophagus usually originate from the inferior thyroid artery, however, other origins are not infrequent

In 125 specimens, esophageal arteries originate from the inferior thyroid artery at three separate sites, viz.: the ascending portion, the descending portion, and terminal rami of the artery (Fig 1-116).

The esophageal arteries originate from the terminal branches of the inferior thyroid artery more frequently than from the ascending or descending portions of the vessel. However, the total number of branches from the latter two segments of the artery exceeds the number derived from the terminal divisions of the parent vessel. Usually a single esophageal branch originates from a segment of the inferior thyroid artery, two, but rarely more, esophageal branches arise from the same or different segments of the thyroid artery. Esophageal vessels that originate from the ascending segment of the thyroid artery not only are larger than similar vessels derived from the terminal branches and the descending portion of the inferior thyroid artery, but they also descend a greater distance on the anterolateral surface of the esophagus In the majority of cases, there occurs a tracheoesophageal vessel which arose from the ascending portion of the inferior thyroid artery, it courses downward in company with the recurrent laryngeal nerve into the superior mediastinum This vessel supplies the trachea and the hilar lymph nodes, additionally, in several instances, the artery establishes a gross anastomosis with the right or left superior bronchial artery Near the level of the suprasternal notch, one to three branches arise from the tracheo-

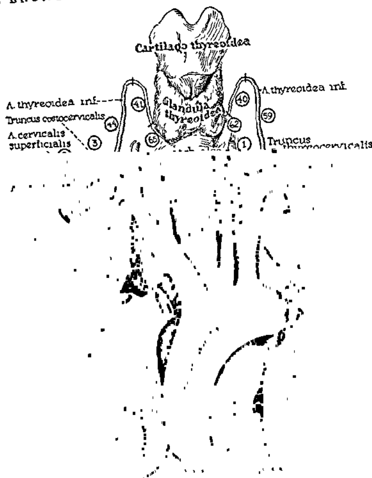


Fig 1-116. Sites of cervical origins of the esophageal arteries in 100 specimens, shown semi-schematically The perpendicular lines that transect each of the inferior thyroid arteries indicate the divisions of the vessel into ascending, descending, and terminal segments The encircled numeral placed either near or on a vessel records the number of instances in 100 specimens studied in which esophageal rami originate from the particular vessel (*From Swigart et al.,* 1950)

esophageal artery to supply the posterolateral aspect of the esophagus Esophageal arteries are found to arise from the ascending segment of the inferior thyroid artery in 36 8 per cent (46 cases) on the right, 51.11 per cent (64 cases) on the left side As already stated, esophageal arteries that arise from the descending portion of the inferior thyroid artery or its terminal branches do not descend very far inferiorly on the esophagus

Although the majority of esophageal arteries take origin from the inferior thyroid artery, there are 13 cases in which the esophageal arteries arise from other sources (Fig 1-116, representing 100 dissections) The addition of 25 dissections, bringing the total of cervical dissections to 125, reveals two cases, on the right side, in which esophageal arteries arise from the ascending pharyngeal artery and the common carotid artery In one case, on the left side, an esophageal artery arises from the left common carotid artery. Thus, in 12 8 per cent of cases (16 of 125 cervical dissections), esophageal arteries originate from sources other than the inferior thyroid arteries.

Thoracic Portion of the Esophagus According to the descriptions in the standard textbooks of anatomy, the esophagus derives part of its arterial supply from the bronchial arteries (Figs 1-117 and 1-118) To these general statements, precise information on the bronchial sources of the esophageal arteries may now be added The patterns observed in a recent study are distributed among nine types (Fig 1-115).

Most frequently there are 3 bronchial arteries, 2 left and 1 right In some specimens, however,

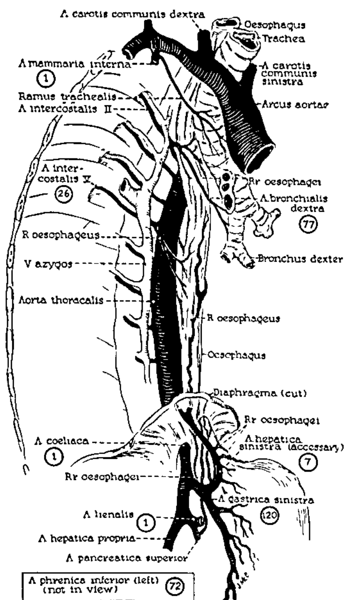


Fig. 1-117. Sites of thoracic and abdominal origins of the esophageal arteries in 125 specimens, shown semischematically A right lateral dissection of the posterior mediastinum and upper abdomen reveals the esophagus and the sources of its vessels of supply. The encircled numbers near the labeled vessel record the frequency of esophageal rami originating from the particular vessel in 125 dissections The text descriptions are based on a study of 150 specimens *(From Swigart et al, 1950)*

there are 2 right bronchial arteries, in such cases the second right bronchial artery courses either ventrally or dorsally to the esophagus The bronchial artery of the ventral surface of the esophagus usually passes anterior to the bifurcation of the trachea, ultimately reaching the inferior border of the right main bronchus

In 72 per cent (108 specimens) of 150 cadavers examined, the inferior left bronchial artery gives rise to esophageal vessels (compare Fig 1-118, 125 specimens). The latter vessels are of slightly smaller caliber than the bronchial arteries, they descend a variable distance on the anterior surface of the esophagus. Anastomoses between these esophageal vessels and the ascending branch of esophageal arteries of thoracic aortic origin occur in many instances Esophageal arteries from the superior left bronchial artery and superior right bronchial artery, 34.67 per cent and 66 67 per cent (52 and 100 cases, respectively, of 150 specimens),

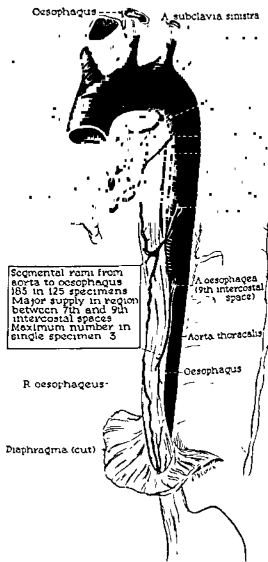


Fig 1-118. Sites of thoracic origin of the esophageal arteries in 125 specimens, shown semischematically. A left lateral dissection of the specimen illustrated in A The level of origins and the course of the left bronchial arteries and esophageal arteries are depicted. The encircled numbers represent the frequency of esophageal rami derived from the several arterial sources in 125 dissections Ascending branches of esophageal arteries from abdominal level and descending branches of the segmental esophageal arteries of thoracic level are shown *(From Swigart et al, 1950)*

ascend on the anterolateral or posterolateral surface of the esophagus. When a second right bronchial artery is present (as an inferior right bronchial artery), esophageal branches derived therefrom supply the esophagus, as the bronchial artery passes either ventrally or dorsally to the visceral tube. In 14 per cent (21 cases), the inferior right bronchial artery gives rise to a vessel of appreciable size, which courses a short distance inferiorly on the right anterior surface of the esophagus. Esophageal arteries of this latter origin rarely form a gross anastomosis with any other esophageal vessel. In fact, the portion of the thoracic esophagus immediately inferior to the lower right bronchus appears to be less well supplied by esophageal vessels than any other portion of the tube.

In 2.67 per cent of cases (4 specimens) there are 3 left bronchial arteries; in each instance, esophageal arteries arise from the middle left bronchial artery.

Right intercostal arteries are the source of origin of esophageal arteries in 20 per cent of the cases studied (30 of 150 specimens, compare Fig. 1-117, 125 specimens). In a single specimen an esophageal artery arises from a left intercostal artery.

Usually an intercostal artery gives origin to a single esophageal artery, however, in 5 specimens, 2 branches arise from the same intercostal artery, and, in 3 specimens, 3 esophageal rami are derived from the same intercostal artery.

Exceptional origins of esophageal arteries occur on the right side in 3 specimens: the internal thoracic artery, the costocervical trunk, and the subclavian artery, each is the source of origin for an esophageal artery. In each instance the vessel courses downward on the anterior surface of the esophagus.

Abdominal Portion of Esophagus. In 142 specimens (94.67 per cent) of 150 specimens examined, the left gastric artery is a source of origin for esophageal arteries (compare Fig. 1-117).

The esophageal arteries originate from the left gastric artery, either just proximal to the point where the vessel reverses its direction to supply the lesser curvature of the stomach, or from the area of the bend itself. These esophageal arteries follow the longitudinal axis of the esophagus, supplying predominately the right anterior and posterior surfaces of the esophagus. Throughout the course of the vessels, under the visceral peritoneum of the esophagus, small branches penetrate the muscular tunic of the viscus.

Of the 142 specimens in which the left gastric artery is a source of esophageal supply, 78 per cent of the cases possess 1 to 3 esophageal arteries derived from the left gastric artery. In but 1.33 per cent (2 specimens) there are as many as 6 esophageal arteries arising from the left gastric.

The left inferior phrenic artery is a source of origin of esophageal vessels in 56 per cent of cases (84 of 150 specimens, compare Fig. 1-117, 125 specimens). In all but 8 per cent (12 specimens of the 84), there is a single esophageal branch. The course of these esophageal vessels is similar to that of vessels arising from the left gastric artery, that is, parallel with the longitudinal axis of the esophagus and through the esophageal hiatus of the diaphragm.

Of the 150 cases, esophageal supply originates from the right inferior phrenic artery in 3.33 per cent (5 specimens). In 1 case there are 2 branches, in each of the remaining 4 cases there is a single branch, distributed to the right posterior surface of the esophagus.

In 10 per cent of the cases (15 of 150 specimens), esophageal arteries originate from an accessory left hepatic artery (compare Fig. 1-117, 125 specimens). With the exception of 3 specimens, only 1 esophageal artery in each instance is derived from the above vessel, however, the main branch divides into 2 or 3 twigs when the esophagus is reached.

In 5.56 per cent of the above 15 specimens (8 cases), no esophageal artery arises from the left gastric artery. In the 8 specimens, the supply to the right aspect of the esophagus is derived from the accessory left hepatic artery. The artery divides in such a way as to send rami to both anterior and posterior surfaces.

In 1.33 per cent of cases (2 specimens), 1 to 2 esophageal arteries originate from the proximal one-third of the splenic artery.

In a single specimen (0.67 per cent), 1 esophageal artery originates from the celiac axis.

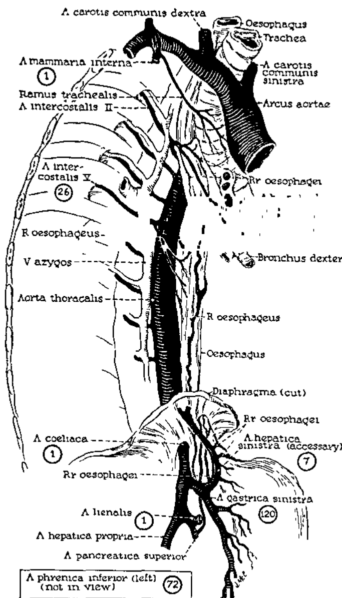


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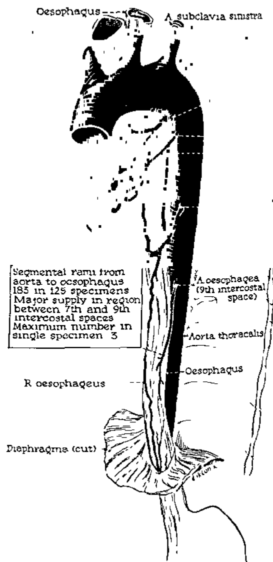


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In a single specimen (0.67 per cent), 1 esophageal *artery originates* from the celiac axis.

Physiology of muscular contraction

W. F. H. M. MOMMAERTS

It is appropriate to start this part of an encyclopedia of cardiology with a description of the physiology of muscle with special emphasis on *striated muscle*. Not only is the myocardium itself a muscle with similar microscopic structure, so that much can be learned from the similarities as well as from the differences, but skeletal muscle has also been the object of choice for many fundamental investigations upon which many current concepts in biochemistry and physiology are based. This preference has been caused largely by the circumstance that, as Meyerhof (1930) has expressed, muscle is the one tissue in which "the transformation of chemical into other forms of energy takes place in a way which can be quantitatively comprehended" And this transformation is, after all, one of the chief problems of biologic investigation

There are many angles from which the activity of muscle can be considered, in this discussion, the problem will be divided into questions of function, structure, and metabolism Such a division is entirely artificial, but will be necessary since we cannot reflect upon the entire problem at once Morphologic, biochemical, and physiologic investigations have progressed for generations, usually quite independently. A truly fundamental approach uniting all these views is more recent, it is exemplified by work on the structure of muscle by a combination of biochemical and optical (including electron optical and diffraction) methods, on the relation between chemical and physical events, or on the interconnection between structural properties and metabolic reactions. However, a true synthesis of all these disciplines still takes place on a highly hypothetic level, since so many of the basic facts are as yet unknown.

Muscle contracts in response to a *stimulus* which can be supplied by an efferent nerve or, in the heart, by foci of automatic activity within its own structure The stimulus brings a given tissue into a state of *excitation*, which, in turn, causes the fibrous structure *to contract*. Unexplained as the nature of the contraction process may be, the mechanism of its preceding evocation by the excitatory event is so unknown to us that we do not even have a serious working hypothesis about it. The speeds with which these events occur differ widely, in relation to the velocity required of their function (Hill, 1949a)

The contraction process involves an expenditure of energy generated by metabolism, over and above that yielded by the resting metabolism of muscle, which presumably serves the maintenance of the tissue with respect, for example, to its ionic composition. The necessity of this increase is obvious when the contraction results in the performance of work, which would then be derived from the energy supplied by this additional metabolism Such added metabolism, however, appears also when no work is done, as would be the case in a contraction without opposing force, or in an isometric contraction This shows that *chemical energy is used to bring the muscle into the active state, whether work is done or not.* The performance of work, however, causes a recruitment of energy in addition to that needed for the activation and the shortening as such.

It has already been implied that the required

work is evident Nevertheless, there are muscle structures which are being stretched by the contracting elements, so that a certain amount of concealed work is done which is dissipated as heat. This stretching affects, not only external passive structures such as tendon, but also an internal element named the "series elastic component." It has been proposed that this is located in noncontractile parts of the sarcomere (Philpot and Szent-Gyorgyi, 1953), and some of its mechanical characteristics have been determined (Wilkie, 1956b).

A stimulus closely following a preceding excitation will again be effective unless it falls within the *refractory period* This period is very brief in skeletal muscle, of the order of milliseconds, very much shorter than the duration of the mechanical cycle Hence, the second *stimulus still* finds the muscle in a state of active shortening, and the activities summate. *In the heart, the duration of total (absolute plus relative) refractory period is of the same order as that of the mechanical cycle, so that summation cannot normally occur* By the summation of a series of stimuli of sufficient frequency, a muscle goes into a steady state of activity, or *tetanus*, by which a greater tension or shortening is developed than *in a twitch It* is believed that a tetanus represents the maximal activity of which a muscle is capable, while in a twitch the fundamental process of activation, also called the active state, declines before the muscle has been able to express this activation macroscopically (Ritchie, 1954, Ritchie and Wilkie, 1955) This is true to a varying extent, dependent on the kind of muscle and the temperature The active state *in a twitch* can be prolonged by epinephrine and by replacing the chloride in the medium by *nitrate*, by which means the twitch tension can be made to approach the tetanic tension These same influences also prolong the negative *afterpotential* of the excitation wave (Edwards, Ritchie, and Wilkie, 1956). The fact that the "amount" of activity obtainable from a single event of excitation *is variable* is of great theoretic importance for the *interpretation* of the link between stimulation and contraction (Hill and Macpherson, 1954), and is also bound to exert a great influence *on* the understanding of cardiac dynamics and its regulation, e g, by epinephrine or digitalis This same variability of the response is also the basis of the type of adjustments of which the classical staircase effect is an example. A renewed interest in this phenomenon has been initiated by Hajdu and Szent-Gyorgyi (1952a) in terms of delicate ion balances which are, in part, regulated by lipid substances in the plasma (Titus et al, 1956), and is currently being analyzed in terms of fundamental mechanical concepts (Abbott and Mommaerts, 1959). In a tetanus, however, regardless of the size of the twitch, the full level of activation is reached and maintained.

Most of the contractions of skeletal muscles in the body are tetani, although there are exceptions to this rule. In coordinated movements, these tetani are not initiated by direct motor activation of the normal muscle fibers, but start with a stimulation of the muscle spindles through small motor (Aγ) fibers, the contraction of the ends of the spindle fibers causes a stretch of their central parts, stimulating their annulospiral nerve endings, which in turn leads to reflex stimulation of the bulk of the muscle through large motor (Aα) fibers (*Kuffler and Hunt*, 1952). According to their innervation by the α fibers, the muscle cells are organized into motor units, comprising from a few to several hundreds of fibers Stimulation *of one nerve fiber* leads to full contraction of the entire motor unit which it innervates, according to the *all-or-none principle;* this full *contraction still* depends, however, on the factors discussed above. *Muscle tonus or submaximal tension development is maintained by asynchronous contractions of alternatingly active fiber groups*

Like any deformable body, a resting muscle develops *elastic tension* when stretched. This elasticity, a part of which may reside *in the* sarcolemma and in connective tissue elements, is comparable to that of rubber, in that the *force* opposing stretch originates in the tend*ency of the* molecular chains of fibrous proteins to assume randomly coiled configurations. The elasticity of a contracted muscle, however, is not rubberlike but normal, suggesting additional molecular bonding in the course of the *contraction* process (Hill, 1953a, Aubert, 1953). Regardless *of* these distinctions, it is possible to measure the force developed as a function of length to obtain the length-tension diagram. This is difficult, experimentally, because of

energy is generated by muscular metabolism. For the organism as a whole, *this metabolism is respiratory or oxidative, consisting of the combustion of carbohydrates, fats, and proteins to carbon dioxide, water, and nitrogenous waste products* However, all muscle can contract anaerobically for shorter or longer times, so that the contraction process itself is not aerobic. The most striking anaerobic metabolic process is *glycolysis*, yet this too can be eliminated without directly abolishing contractile performance. In the absence of these two processes, prolonged activity proceeds at the cost of splitting so-called energy-rich phosphate compounds such as *phosphocreatine* and *adenosine triphosphate* (*ATP*). A dominant theory of muscle action is, therefore, that the splitting of one of these substances is the energy-yielding reaction and the direct cause of contraction. This theory has been eminently satisfactory because biochemical investigation has shown that respiration and glycolysis both result in a synthesis of these high-energy compounds from their breakdown products (aerobic and anaerobic phosphorylation) and so will resupply the active tissue with its immediate energy sources to the extent that they are used up on activity With a remarkable anticipation of these recent insights, the high-energy phosphate has been termed "the coinage of the living cell" (Szent-Gyorgyi, 1937).

Morphologically, the contractile activity of striated muscles is assigned to their *fibrils* These are composed of proteins, among which *myosin* and *actin* constitute the bulk Both these proteins have intricate relations to adenosine triphosphate, which lend substance to the view that the interaction between this substance and myosin and actin (perhaps in the form of their complex, *actomyosin*) constitutes the final mechanism of contraction An especially impressive experimental demonstration of this is Szent-Gyorgyi's discovery of actomyosin filaments or extracted muscle fiber preparations which contract upon the addition of ATP in a suitable ionic medium.

PHYSIOLOGIC ASPECTS

As treated at greater length in monographs of physiology (Wilkie, 1954), a single contraction cycle (*muscle twitch*), consisting of a contraction and a relaxation phase, is elicited by a *stimulus*. Present concepts regard the stimulus as a propagated reversal of the polarity of a surface membrane (Hodgkin, 1951), although the polarization phenomena can be looked upon in terms other than membrane effects. Ingenious experiments by Huxley and Taylor (1955) indicate that the membrane event is conducted inward to the myofibrils by the Z membranes which, bisecting the I bands, form sheets across the muscle which have a certain continuity and which are attached to the sarcolemma.

The mechanical response is separated from the stimulus by a *latency period*, during the approximate span of which a number of events take place, which may be expressions of the coupling between stimulation and activation In its earliest part is the *action potential* of the impulse itself, accompanied by impedance changes, but, contrary to what happens for nerve, these impedance changes outlast the action potential and merge with changes associated with contraction itself (Dubuisson, 1937). After the absolute latency period, of the order of milliseconds, the muscle first shows a minute slackening prior to its contraction. It is disputed whether this latency relaxation is a property of the contractile matter (Sandow) or of the sarcolemma (Abbott and Ritchie, 1951; Hill, 1951). At approximately the same time, there is a minute constriction of the total volume, the *Ernst effect*, amounting to not more than 0.02 mm/3 Gm muscle (Ernst) probably attributable to electrostriction due to a temporary release of ions. There are also optical changes, with respect to light scattering, diffraction, and birefringence, but these have been difficult to interpret. The absolute lengths of the latency period, contraction phase, and relaxation phase differ for various muscles, in relation to their various speed characteristics The total duration of the cycle is about 0.1 sec for a frog sartorius at room temperature, and even less for mammalian muscles *in situ*. The cardiac cycle in larger animals is much slower, but in small birds, for example, the velocity of cardiac systole is fully comparable to that of fast skeletal muscles

In an *isotonic twitch*, the muscle shortens and work is performed to the extent that weights are lifted or forces displaced. In an *isometric twitch*, there is development of tension without gross shortening, and no external

work is evident. Nevertheless, there are muscle structures which are being stretched by the contracting elements, so that a certain amount of concealed work is done which is dissipated as heat. This stretching affects, not only external passive structures such as tendon, but also an internal element named the "series elastic component." It has been proposed that this is located in noncontractile parts of the sarcomere (Philpot and Szent-Gyorgyi, 1953), and some of its mechanical characteristics have been determined (Wilkie, 1956b).

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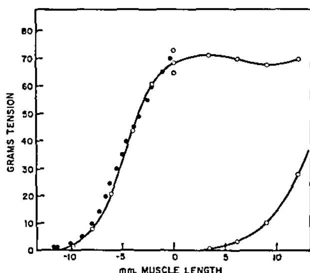


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hysteresis and differences in force developed isometrically and isotonically at a given length. Painstaking work by Wilkie (1954) with the frog sartorius muscle has largely eliminated these difficulties, and the results may be taken to illustrate the general behavior (Fig. 2-1) Usually, the length of the muscle in the body is such that there is no tension at complete rest and the maximal tension is generated upon stimulation. Both at greater and at lesser length, less tension would be actively developed. When muscles are tetanized isotonically, it is obvious that they will contract until they reach a length corresponding to a force equal to the weight attached to them (see Fig. 2-1). If this load is small, shortening will be nearly maximal, but very little work will be done, since the displaced force is small. With a very large load, work will be small too, because of the short distance of displacement. Maximal work is performed at some intermediary load, at which the product of force and shortening is greatest This is not a physiologic regulation characteristic for muscle but a simple mechanical rule, of course, the accurate shape of the work-load curve depends on the tension-length curve These phenomena are basic to determining the work done by the heart also Increasing the load in isotonic contraction will decrease also the velocity of shortening The force-velocity curve of muscle has often been expressed by the equation

$$(P + a)(V + b) = (P_o + a)b$$

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This equation and further derivations based upon it are of great use in quantitatively describing the behavior of muscle (Wilkie, 1956a). Considerable significance has been attached to the constant a, which is identical with one obtained from the proportionality between shortening heat and extent of shortening (Hill, 1949a, 1950), but an exception to this equality has recently been discovered (Abbott and Lowy, 1956). The maximal isometric tensions do not differ greatly for various muscles, 1 to 2 kg/cm² cross section, but the velocity scales vary enormously, especially when *smooth muscles* also are drawn into the comparison. *In the latter case, the contractile state persists so long that infrequent stimulation can maintain tension.* Since each activation process represents a roughly constant amount of energy (Mommaerts, 1950), also for smooth muscle (Csapo and Gergely, 1950), it is obvious that the economy of tension maintenance varies inversely with the speed of the muscle Similarly, the economy for a given muscle is greater at lower temperature. When the speed of contraction is controlled, voluntarily or otherwise, it is found that an optimum speed exists at which both the efficiency of the muscle and the power output are about maximal. An interesting question has been raised (Hill, 1956) with respect to the heart, the speed of which increases during the transition from rest to effort. In which state does it function optimally? Or can it change its velocity characteristics to fit the conditions?

When a muscle is driven to contract for a long time, a state will set in, in which its mechanical responses first diminish and eventually fail. This is known as *fatigue* and is, in the isolated muscle, associated with *an accumulation of lactic acid and a diminution of adenosine triphosphate and phosphocreatine.* In the whole body, progressive failing of the muscle can also be due to *synaptic* or *central fatigue.*

but Merton has shown that fatigue is more exclusively a property of muscle itself than has frequently been believed. An important question is why some muscles fatigue readily, others, like the heart, not at all. This difference has a metabolic basis (Chap. 2).

Since muscle contraction is a conversion of chemical into mechanical energy, one would expect the phenomenon to be accompanied by thermal changes. These could occur for two rather different reasons. In the first case, a certain amount of energy would serve to perform some form of work (e.g., mechanical or osmotic) which would subsequently (or even simultaneously) degenerate or dissipate, being quantitatively converted into heat; this will be called dissipational heat production, and is always exothermic. *Dissipational heat* will also develop when work is performed with an efficiency below the ideally possible one, as is always to some extent the case in actuality. In the second case, the heat effect is a necessary accompaniment of the energy transformation as such, because, in this process, *owing to a change in entropy, the heat effect* (ΔH) and free-energy effect (ΔF) *are not equal. This* phenomenon, which will be called *obligatory heat*, can be either positive or negative: if the free-energy change exceeds the heat content change, the reaction will be endothermic, since heat is drawn from the surroundings.

Experiments on the course of the heat production in muscle activity have been pursued for a generation with ever-increasing perfection by Hill. Such myothermic studies have the great significance of providing a quantitative *measure* of the intensity of the energy exchange processes. Its relation to these processes is un*specific*, which is at once a strength and a weakness: a weakness, because the measured heat changes cannot be explicitly identified with specific chemical reactions, a strength, because myothermic measurements provide a rigid frame of reference to which proposed chemical mechanisms *must conform*.

Resting muscle shows a steady heat production of low intensity, called the *resting heat*. This is dissipational heat, largely because the basal metabolism of the tissue serves to accumulate ions against a diffusion gradient, while this osmotic work is continually dissipated into heat owing to the leakage of these ions back into the extracellular fluid. The resting heat and the resting respiration which corresponds to it depend on influences such as stretching the muscle (Feng, 1932) or changing the ionic composition of its bathing fluid (Solandt, 1936).

In contractile activity, one must distinguish between initial heat, associated with the activity itself, and the recovery heat, indicative of the chemical restitution processes taking place after it (Hill, 1924). The total amount of heat developed in the aerobic recovery phase is roughly equal to the total energy output in the initial phase, although it is protracted over a much longer time (Hill, 1939), *dependent*, of course, on the temperature, but also on the nature of the preceding activity. *Anaerobically*, the recovery heat is far smaller, often nearly zero, dependent again upon the nature and circumstances of the activity. For example, no measurable anaerobic recovery heat occurs after single twitches, while it does occur after *tetanic activity of frog muscle* at room temperature. This might well indicate that different chemical processes occur in prolonged and in single periods of activity. The difference between aerobic and anaerobic recovery heat indicates that anaerobic phosphorylation occurs with greater thermodynamic effectiveness than aerobic phosphorylation. In its time course, the *recovery heat follows the recovery respiration* accurately (D. K. Hill, 1940a).

The *initial* heat has several components, which may, of course, have mechanisms *in* common. The *activation* or *maintenance heat* is correlated with the onset and decline of the *active state*, and with its prolonged maintenance in a tetanus (Hill, 1953a). Its time *course* should be identical with that of the active state, but in reality some discrepancies *are noted*. When the muscle shortens, a *shortening heat* is developed, in *addition* to the heat of maintenance. The proportionality between heat and shortening is expressed by the same constant *a as was previously* encountered in Hill's equation of the force-velocity relation. The *relaxation heat* appears during relaxation, but it merely represents the return to the muscle of the work performed in contraction, and it vanishes when this return is prevented by catching the lifted weight so that it can *do* no work upon the muscle. When muscle is stretched during its contraction (as frequently happens in the body), the work exerted upon

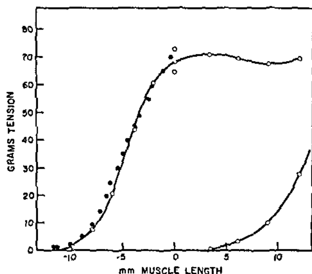


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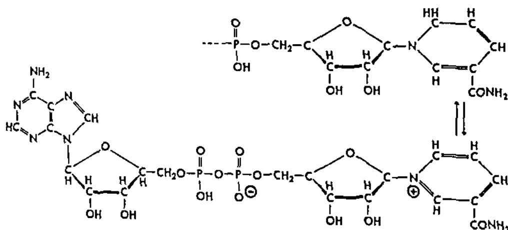
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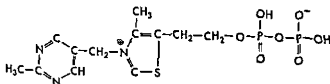
on the early work of Meyerhof The work of Hill on the heat production in muscle was also interpreted in terms of the formation and removal of lactate.

Resting muscles usually contain a small amount of *lactic acid*, of the order of 0 002 M. Additional lactate may be formed from glycogen to a final concentration of 0 04 to 0 06 M by anaerobic stimulation of isolated frog muscle until fatigue sets in, in anaerobic rest, or in rigor These maxima are determined by a self-inhibition of activity and metabolism by acidification and otherwise, which indeed is the mechanism of fatigue or rigor under those conditions When muscles are suspended in bicarbonate and sufficient time is allowed, still more lactate can be formed and all glycogen broken down.

When a muscle engages in a brief period of activity and forms lactic acid in the course of this period, because of anaerobic conditions imposed by the experimenter or, in vivo, by insufficient circulation or because of its own relative lack of oxidative enzymes, it will then oxidatively remove this lactate during its subsequent recovery period. Meyerhof discovered that the oxygen used accounts for the oxidation of only about one-fifth of the lactate removed; the remainder is reconverted into glycogen This is referred to as the *Meyerhof cycle* and operates only in isolated frog muscle. In *mammalian muscle in situ*, the lactate diffuses into the blood stream and is converted into glycogen by the liver; the muscles then recover the used carbohydrate from the blood stream. This is referred to as the *Cori cycle*. Furthermore, it was found in isolated muscles that, during anaerobic activity, the carbohydrate breakdown (judged by lactate production) is about five times greater than the degree of carbohydrate breakdown under aerobic activity (judged by oxygen consumption). This is a general phenomenon in nature, known as the *Pasteur effect*, for which several mechanisms have been suggested (Dickens, 1951).



Diphosphopyridine nucleotide



Thiamine pyrophosphate

Thus the "lactic acid theory" states that, under all circumstances, the primary chemical reaction in contractile activity is a formation of lactic acid, and that this causes contraction by some form of physicochemical interaction with specific loci in the structure of the fibril (Meyerhof, 1930). In experiments of long dura-

it does not appear as heat, so that work must have been absorbed into some other form or must have prevented a corresponding amount of metabolic heat from being generated. When a muscle not only shortens but also performs work, it is found that the contraction heat is unchanged. This important fact, known as the *Fenn effect*, means that the total energy output in contraction is not constant, but that the normal energy release, as expressed by activation and shortening heats, is augmented by the work performed. This additional energy, which may amount to about as much as the contraction heat itself, appears as relaxation heat when the lifted load is permitted to fall back, and remains as undissipated work if the lifted weight is caught at its highest point Whether the Fenn effect is due to a regulative process or to some inherent property of the topochemical mechanisms operative in contraction is unknown The underlying processes may also be related to the absorption of work in a stretched contracting muscle (the *Abbott-Aubert effect*), as referred to previously

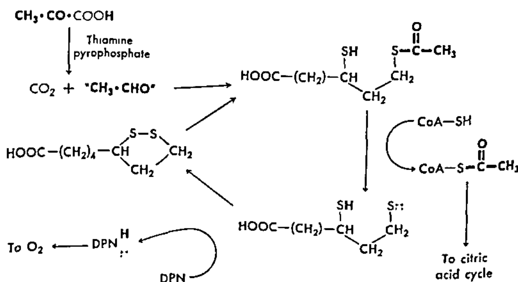
The ratio of the actual work performed to the total energy output is called the *efficiency of the process*. This efficiency, in favorable circumstances, may be about 20 to 25 per cent (Hill, 1939), not unlike that of the heart (Evans, 1936, Bing et al, 1949) Since about half the energy is dissipated in the aerobic recovery process, the efficiency of the initial events themselves is about twice as high Since the activation and shortening heats appear in any case and are therefore wasted, and since any work performed is not accompanied by additional heat, it might even be stated that the fundamental event leading to external work is 100 per cent efficient, although it would require actual knowledge of the mechanisms to permit judgment whether this last statement is not highly artificial or even incorrect. At any rate, the efficiency is so high as to place definite limitations on any proposed theory for the mechanism of contractility.

This very brief description of the major biophysical aspects of the contraction process has been given with but little reference to the corresponding properties of the heart, which have not been studied to the same degree Further investigations in that direction should be very beneficial for the understanding of myocardial function and its pathologic aberrations.

GLYCOLYSIS AND OTHER CHEMICAL REACTIONS WHICH ACCOMPANY CONTRACTILE ACTIVITY

The energy requirements of muscular activity are ultimately provided by respiratory metabolism. Experimentally, however, all muscles can support their activity for a shorter or longer interval without oxygen by *glycolysis*, and in the body, too, such anaerobic activity may occur either locally or temporarily.

Until other chemical processes were recognized, it was believed that glycolysis was the fundamental chemical activity of muscle and the immediate cause of contraction. Investigations beginning with the publication of Fletcher and Hopkins (1907) found expression in the "lactic acid theory" of muscular activity, based

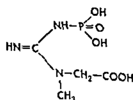


cept for certain coenzymes whose significance in the total picture is restricted to their particular reaction and which are, therefore, neglected here), there are reaction steps which lead to an obligatory coupling with other chemical events These can be oxidoreductive or phosphorylative steps, or both The oxidoreductive steps (reactions 7 and 12) balance, so that there is no over-all oxidation or reduction in the process: $C_6H_{12}O_6 \rightarrow 2C_3H_6O_3$, or: $(C_6H_{10}O_5)_n \rightarrow 2nC_3H_6O_3$ These reactions take place by means of a reversible redox coenzyme, cozymase, or diphosphopyridine nucleotide (DPN) (diagram of the lactic acid cycle). This oxidizes phosphoglyceraldehyde to phosphoglyceric acid (7) and is in turn reoxidized (12) by pyruvate to form lactate It will be seen later that in the alternative event of respiration, the reduced DPN generated in reaction (7) is not reoxidized by pyruvate, but that both DPN and pyruvate are oxidized by the respiratory reaction chain, so that no lactate is formed Otherwise, the same reactions as those given here also form the basis of respiration.

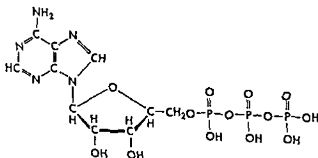
The participation of phosphate starts right at the beginning of the reaction scheme, with the initial *breakdown of glycogen* This could, as in digestion, be attacked by hydrolysis to glucose, but simple consideration will show that phosphoric acid or phosphate, as a substituted form of water,

HOH	HOR
Water	Substituted water

can carry out an analogous process called *phosphorolysis*, which leads directly to glucose-1-phosphate instead of glucose The enzyme catalyzing this process, *phosphorylase*, presents



Phosphocreatine



Adenosine triphosphate

interesting features which may undergo modification in relation to the functional state of the tissue (Cori, 1956) or the action of sympathomimetic agents (Sutherland, 1956). When glucose enters into the reaction (in order to be glycolyzed or converted into glycogen), it likewise has to be phosphorylated, but, contrary to the previous case, the equilibrium of the reaction would not permit direct esterification by inorganic phosphate. Instead, the enzyme *hexokinase* catalyzes phosphorylation by a phosphate donor, *adenosine triphosphate* (ATP), which can force the phosphorylation by virtue of properties to be discussed below.

From the glucose phosphates on, the other [illegible]

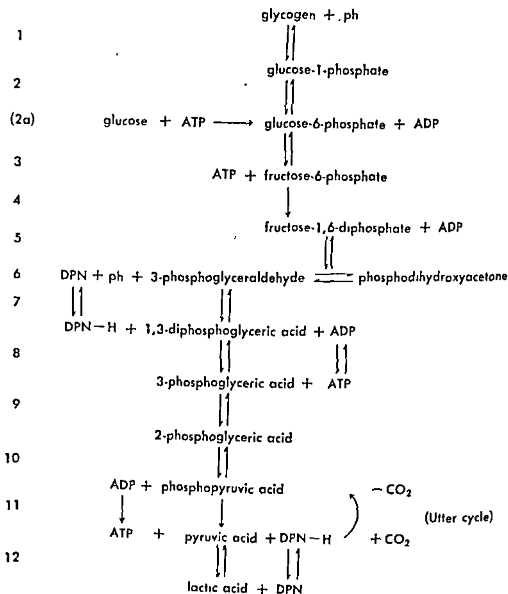
coupled with the oxidation of phosphoglyceraldehyde, in a reaction whose mechanism is of considerable interest (Racker and Krimsky, 1952, Velick, 1953), and which leads to the formation of a phosphate radical which is transferred into *adenosine diphosphate* (ADP) to form ATP. As a result of the further transformation of phosphoglyceric to phosphopyruvic acid, the remaining phosphate radical likewise acquires the property which enables it to be transferred to ADP These transfer reactions, then, serve to regenerate the ATP that is used partly in order to phosphorylate the reactants initially in steps (2*a*) (if occurring) and (4), and partly in processes to be mentioned later This participation of phosphate

$HO{-}HPO_3^-$ or $HO{-}PO_3^=$
Phosphate

radicals takes a central place in the mechanism and links the main pathway to accessory reactions involving other phosphorylated compounds.

The first of these compounds, *phosphocreatine* (PC), was discovered as the result of

tion with minced muscles, it was indeed found that glycolysis accounts approximately for the heat production and seems to be the exclusive by respiration and glycolysis. To identify these sources, one must first pay attention to the chemical mechanisms of glycolysis.



Glycolytic pathway

or preponderant reaction, at least in the over-all balance. In experiments with contracting muscles, however, it was found that *more heat is generated than can be accounted for by glycolysis* This would indicate that, in physiologic activity, other energy-producing reactions come to the fore.

An important change in outlook took place in 1930 at which time Lundsgaard discovered that after poisoning with iodoacetate, anaerobic glycolysis is completely inhibited, yet muscles so treated can perform a certain amount of work. This shows that lactic acid cannot be the cause of contraction and that sources of energy must exist besides that supplied directly

Investigations of various workers (1932–1948) gradually led to the recognition of a pathway of glycolysis shown in the diagram of the lactic acid cycle. The main part of this diagram illustrates the chain of events leading from glycogen (or glucose) to lactic acid. This accounts for the main aspect of the over-all change known as glycolysis, in the course of which a certain amount of chemical energy is set free. Of equal importance, however, are *certain* stoichiometrically associated reactions Their general significance is that, besides those intermediary reactions which consist of molecular fissions or rearrangements which proceed without the participation of other systems (ex-

of ATP by a special enzyme, ATPase, would be such an energy-yielding reaction, but it is doubtful whether mere hydrolysis would yield anything else but heat But, however formulated, the view that some manner of breakdown of ATP furnishes the energy of contraction has been the major theory for some 20 years.

When in the aerobic restitution phase lactate is reconverted into glycogen according to the Meyerhof reaction, the main mechanism consists of a constant supply of ATP by respiration, so that the same reaction scheme is now followed backwards. All individual reaction steps are sufficiently reversible to permit this [apart from reaction (4), which can be aided by a phosphatase hydrolyzing hexose diphosphate without involving ATP], with a major exception in reaction (11) This equilibrium is situated so far toward the formation of ATP and pyruvate that it would not take place spontaneously in the opposite direction An important discovery by Utter (Utter and Kurahashi, 1954) indicates a pathway involving temporary incorporation of carbon dioxide to accomplish this reversal, but its role in muscle metabolism has not yet been investigated.

RESPIRATION AND AEROBIC PHOSPHORYLATION

The discussion of glycolysis has shown how the cell utilizes a complex sequence of chemical reactions for a specific purpose, the generation of high-energy phosphate compounds This process of anaerobic phosphorylation is efficient in the sense that the largest part of the free-energy change in the glycolysis process is laid down in the formation of compounds like ATP. However, it is ineffective in the sense that only a small fraction of the energy is gained which the foodstuffs could yield in a more profound mode of utilization, viz, the complete oxidation to carbon dioxide and water, which is the preferred mode of metabolic utilization of foods. Respiration likewise proceeds in a way which implies a coupling with phosphorylative processes, and which, in keeping with the much larger energetic effects, permits a much greater yield of high-energy phosphate The oxidation of 1 mole glucose, for example, yields about 36 moles of energy-rich phosphate, compared to the two moles gained in glycolysis. This complex process is based upon carbohydrate oxidation, but fats are also utilized, oxidation of amino acids is also important, after more or less indirect pathways of de- or transamination and other preparatory reactions, these finally give rise to substances common to fat- or carbohydrate metabolism. However, the limited knowledge about the role of protein metabolism in muscle or heart discourages a detailed discussion of this matter.

Whether starting from glycogen or from glucose, the initial reactions with which we are concerned are those of *glycolysis*. It is characteristic of glycolysis that the preliminary oxidative step (reaction 7) is effected by DPN, and that the reoxidation of the DPN–H, so formed, occurs by the reduction of pyruvate to lactate. In this fashion, there is a constant cycle DPN ⇌ DPN–H, and no over-all oxidative or reductive change appears in the process In respiration, however, the DPN–H formed in reaction (7) is oxidized by a chain of oxidative enzymes, eventually by oxygen There is nothing, then, to reduce the pyruvate formed in reaction (11), and to cause lactate formation, neither does pyruvate accumulate, but it, too, is metabolized further and is completely oxidized to carbon dioxide and water Hence, there are two new problems the oxidation of DPN–H formed in the oxidation of phosphoglyceraldehyde (and in several other oxidations, as will be seen), and the oxidation of pyruvate

Present knowledge about the catalysis of respiration rests heavily upon the unique discoveries of Warburg, who, by indirect spectroscopic methods, found that the oxidative enzyme directly reacting with oxygen is an *iron-porphyrin compound*, and upon the penetrating spectroscopic observations of Keilin, who demonstrated that cells generally contain several such compounds, named *cytochromes a, b, and c*, which can be seen to undergo changes during the respiratory metabolism of the cells One of these, cytochrome c, can be isolated, and a great deal of chemical work has been done on its chemical constitution It is generally held that Warburg's oxidative enzyme (also known as *cytochrome oxidase* and now detected by direct spectroscopy and recognized as cytochrome a_3) is the one compound, or a major compound, which immediately reacts with oxygen, whereby its bivalent iron is oxidized to the trivalent state, and is reduced again when it exerts its oxidizing effect

careful observations on certain peculiarities of the analytic determination of phosphate in muscle extracts, leading to the recognition of a labile phosphate compound named *phosphagen* (Eggleton, 1939), identified as phosphocreatine by Fiske and Subba Row (1929). The term phosphagen could now be redefined to mean any substance, regardless of its behavior in phosphate analysis, occurring in measurable amount in muscle, which can donate a phosphate group to ADP by means of enzymes contained in the tissue of its occurrence. Shortly after the discovery of phosphocreatine, it was found that upon its hydrolysis, a rather large amount of heat, some 12,000 cal/mole, is liberated. Since phosphate esters generally yield much less heat than that, the insight began to develop that PC is a substance which, through its breakdown, can make a large amount of energy available. Even though the difference between heat change and free-energy change had to be kept in mind, PC now demanded consideration as an energy-supplying substance for muscular activity This became a major theoretical view when Lundsgaard, as discussed above, demonstrated that in the alactacidogenic activity of the iodoacetate-poisoned muscle, a gradual exhaustion of PC progresses during the contraction series, and that approximately at the moment of its depletion, contractile activity stops Phosphocreatine, then, seemed to be directly related to the mechanism of contraction, while glycolysis and respiration now appeared as processes which are not directly involved in activity but which can cause the resynthesis of PC (Nachmansohn, 1928) by processes now known as anaerobic and aerobic phosphorylation This new theoretical viewpoint was exposed in an important article by A V Hill in 1932

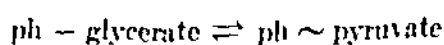
Further work on the enzymatic mechanisms of phosphorylation and of the breakdown of PC would soon suggest, however, that this substance is relatively remote from the main metabolic pathways For example, Lohmann found that the enzymatic hydrolysis of PC in aqueous muscle extracts does not proceed directly, but by subsequent steps with separate enzymes, creatine kinase and adenosinetriphosphatase (ATPase), respectively.


PC + ADP ⇄ creatine + ATP (1)

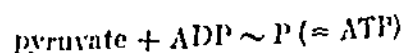

ATP → ADP + phosphate (2)

Similarly, none of the glycolytic steps indicated in the citric acid cycle (or of the aerobic reactions) can effect a direct phosphorylation of creatine; they all generate ATP (or other nucleotide triphosphate such as guanoside triphosphate) which can exchange phosphate with ADP-ATP by means of the enzyme nucleoside diphosphate kinase (Berg and Joklik, 1954), which in turn can make PC by means of the reversible reaction (1), called the *Lohmann reaction*. As a result of these developments, one began to look upon ATP as the substance most closely related to contractile activity, and the meaning of metabolism revealed itself as a mechanism to resynthesize ATP to the extent that it is used in the activity of the tissue.

A systematic survey of the entire field led Lipmann (1941) to develop the concept of "energy-rich phosphate compounds" These are substances such as ATP, PC, phosphopyruvate, and others, in which the phosphate radical is bound in such a way that upon fission of the bond in a hydrolytic or transfer reaction, the free-energy effect of the process is considerable The actual values of these energy effects (and also of the heat effects which, although not identical, frequently show a general parallelism) are subject to constant revision, and are probably in the vicinity of 7000 cal/mole Glycolysis can be described then as a process in which, because of chemical changes in other parts of the phosphorylated reactants, the phosphate radicals contained in these assume high-energy character (often denoted as ~ph) so that they become transferable onto ADP, e.g., in reactions (11) and (12).

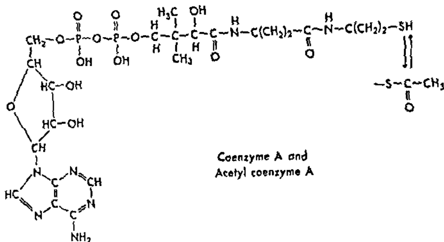

ph − glycerate ⇄ ph ~ pyruvate


ph ~ pyruvate + ADP →


pyruvate + ADP ~ P (= ATP)

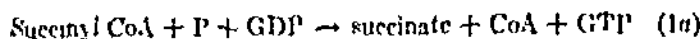
In the reaction, glycerate → pyruvate, energy would be liberated, by performing the same reaction with the corresponding phosphorylated compounds, this energy becomes captivated as ~ph, eventually in the form of ATP. This substance, in turn, can participate in reactions in which a "driving force" is needed [such as the phosphorylation of glucose, reaction (1)], or can, presumably, participate in the mechanochemical reactions leading to contraction It has often been considered that the hydrolysis

carbon fragment has been oxidized to carbon dioxide and water. The nature of the "active acetyl" was a major problem for a number of years, it became solved on the basis of the discovery of *coenzyme A*, or coacetylase, a coenzyme for acetylation processes

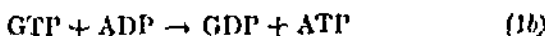


The formation of citrate from oxaloacetate is not strictly, an acetylation, since the added acetyl joins with the CH_3, rather than with the carboxyl group, but coenzyme A apparently effects both kinds of activation. The initiation of the citric acid cycle was therefore elucidated when "active acetate" was identified as acetyl-coacetylase (its sulfhydryl group being acetylated), and when it was shown that acetyl coenzyme A reacts with oxaloacetate to form citrate, under the influence of crystalline condensing enzyme. To understand the utilization of pyruvate, it must first be remembered that in all decarboxylative reactions of that substance (and of α-keto acids in general), thiamine pyrophosphate acts as a coenzyme. In a manner not agreed upon in detail, involving a cyclic participation of an additional sulfhydryl coenzyme, lipoic acid (diagram of lipoic acid cycle), and catalysis by a complex enzyme called pyruvate dehydrogenase, this results in the elimination of carbon dioxide and the formation of acetyl coenzyme A. Hence, through this sequence of preliminary reactions, and of the citric acid cycle itself, pyruvate is completely oxidized.

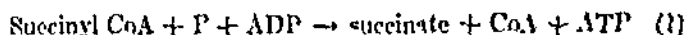
Among the individual steps of the citric acid cycle, the oxidation of α-ketoglutaric acid to succinic acid must be considered briefly. It has certain features in common with the oxidative decarboxylation of pyruvate, likewise involving thiamine pyrophosphate and lipoic acid, and leading, analogously, to succinyl coenzyme A as the primary product. This undergoes the following reactions.



$$\text{Succinyl CoA} + \text{P} + \text{GDP} \rightarrow \text{succinate} + \text{CoA} + \text{GTP} \quad (1a)$$



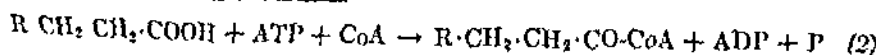
$$\text{GTP} + \text{ADP} \rightarrow \text{GDP} + \text{ATP} \quad (1b)$$



$$\text{Succinyl CoA} + \text{P} + \text{ADP} \rightarrow \text{succinate} + \text{CoA} + \text{ATP} \quad (1)$$

Apart from the additional point that guanosine diphosphate or inosine diphosphate rather than adenosine diphosphate is the primary phosphate acceptor, here is an example of the generation of a high-energy phosphate in the course of a respiratory reaction. However, its mechanism is unique, and is not representative for aerobic phosphorylation at large.

Just as carbohydrates, via pyruvate, enter the oxidation cycle in the form of acetyl coenzyme A, fatty acid oxidation similarly makes use of this pathway. This involves first the formation of a long-chain acyl coenzyme A:

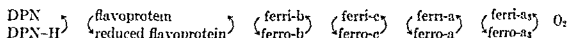


$$\text{R}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{COOH} + \text{ATP} + \text{CoA} \rightarrow \text{R}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO-CoA} + \text{ADP} + \text{P} \quad (2)$$

then beta oxidation to form acetyl CoA and the CoA derivative of the next lower fatty acid:

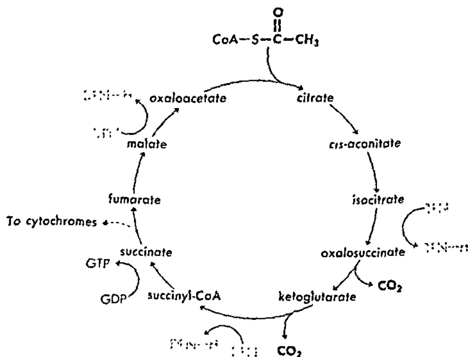
upon the next member of the chain. Cytochrome oxidase is affected by poisons such as cyanide and carbon monoxide, which inhibit cell respiration. The member which is oxidized by the oxidase is cytochrome a, which oxidizes c, and this in turn oxidizes b The latter enzyme still does not react with any substrate molecules, but oxidizes one of a group of yellow enzymes, or *flavoproteins* (oxidative enzymes having a derivative of vitamin B_2 as their reactive group) (Warburg and Christian; Theorell, 1956), in this case called DPN-cytochrome reductase.

The entire enzyme chain for the oxidation of DPN is shown schematically as follows:



Direct information about the sequence of action of the cytochrome components has been obtained with highly perfected optical methods This reaction system explains the oxidation of DPN–H, and hence the oxidation of all substances, such as phosphoglyceraldehyde, which reduce DPN. Other substrates require a similar coenzyme, TPN (differing from DPN by an additional phosphate radical), and this is thought to be oxidized by the same chain of enzymes, beginning, however, with a TPN-cytochrome reductase. However, the oxidative action of DPN or TPN leads only to the removal of two hydrogen atoms from the substrate molecule, and does not explain the catabolism of the remaining part of the molecule, notably its carbon chain

After significant investigations by Szent-Györgyi (1937), which revealed the catalytic role of C_4-dicarbonic acids in cellular respiration, and after discovery of the formation of succinic from citric acid (Martius and Knoop, 1937), it remained for Krebs (1937) to discern a cyclic mechanism of conversions of these substances called the *citric acid cycle* (*Krebs cycle*), leading to the combustion of a molecule of pyruvate The outline of the present and, apparently, final form of this cycle is presented in the accompanying diagram A number of detailed questions arises.

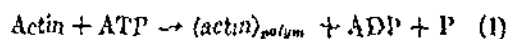


Citric acid cycle

The cycle starts with a condensation of oxaloacetic acid (generated as the end product of the cycle) with an "active acetyl" group, generated from pyruvate or other fuels, to form citrate A series of dehydrogenation (oxidation) and decarboxylation steps leads back to oxaloacetate, so that in the process the added 2-

cules with a length of 0.16 μ and with a molecular weight of 420,000. By means of controlled tryptic digestion, myosin can be decomposed into a *light* and a *heavy meromyosin*, of which the latter retains the ATPase activity and the property of combining with actin. Each of these components consists of further subunits, called protomyosins.

Actin is a protein that has the remarkable property of occurring in two different molecular configurations, called globular (G-) and fibrous (F-)actin. The G-F *transition* is a polymerization process, elicited by salt, and ATP is required for its occurrence and for the stabilization of G-actin. It has been purified by ultracentrifugal isolation of the polymer followed by its reversible depolymerization in the presence of ATP. Studies on the pure protein showed that the polymerization process entails a mole-for-mole breakdown of ATP in a stoichiometric reaction



$$\text{Actin} + \text{ATP} \rightarrow (\text{actin})_{polym} + \text{ADP} + \text{P} \quad (1)$$

and the amounts in living muscle are such that this reaction could quantitatively account for the energy liberated in a muscle twitch (Mommaerts, 1951). F-actin forms long molecular strands, formed by linear association of G-actin molecules.

The properties of myosin and actin, and of actomyosin (see below), have been studied chiefly on preparations obtained from rabbit skeletal muscle, but enough scattered observations are available to illustrate that their occurrence is a general characteristic of muscles, including the heart (Benson et al., 1955; Sobel et al., 1955). In a fresh heart preparation, myosin does not occur but is replaced by another protein of lower molecular weight (this is not generally accepted).

The two proteins myosin and actin can combine to form the complex, *actomyosin*.



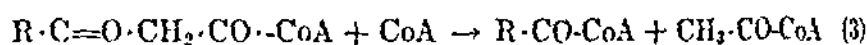
$$\text{Myosin} + \text{actin} \underset{}{\overset{(\text{ATP})}{\rightleftharpoons}} \textit{actomyosin} \quad (2)$$

Presumably, myosin molecules attach themselves randomly to actin strands (Fig. 2-2), since in solution no forces are present to direct a more specific arrangement. ATP effects a reversal of the combination reaction, thus causing physical changes in actomyosin solutions, such as reductions in viscosity or turbidity, which can be used for the quantitative study of various aspects of interaction between actomyosin and ATP. These interactions display particularly interesting manifestations when the actomyosin, instead of being dissolved, occurs in the gel condition, at an ionic composition not unlike that of the intracellular cation medium. According to a discovery by Szent-Györgyi (1942), such systems contract with ATP. Flocculated actomyosin shows a syneresis of the individual aggregates ("superprecipitation"), and unoriented actomyosin threads become shorter and thinner while losing mechanical strength. Oriented threads and fibers obtained from surface-spread actomyosin shorten longitudinally and can lift weights. Fiber preparations can be obtained by treatment of muscle bundles with aqueous glycerol, which leaves the actomyosin in place while removing most other components; these contract longitudinally and develop a tension comparable to that of living muscle.

Finally, an extracted preparation has now been obtained (Guillory and Mommaerts) which can contract as well as respire, and



Fig. 2-2. Schematic diagram of actomyosin micelles in solution. (Note, the actual number of myosin rods is greater than is drawn here.)

$$R\cdot CH_2\ CH_2\cdot CO\text{-}CoA \rightarrow R\cdot CH{:}CH\cdot CO\text{-}CoA \rightarrow R\cdot CHOH\cdot CH_2CO\text{-}CoA \rightarrow$$
$$R\cdot C{=}O\cdot CH_2\cdot CO\cdot\text{-}CoA + CoA \rightarrow R\cdot CO\text{-}CoA + CH_3\cdot CO\text{-}CoA \quad (3)$$

This goes on until the entire fatty acid chain is oxidized, unless the last stage, that of acetoacetyl CoA, is directed otherwise by splitting to form acetoacetate. This, however, is not the normal pathway for muscular tissues. Rather, these tissues tend to oxidize free acetoacetate, after prior formation of its CoA derivative. Inasmuch as fatty acid metabolism terminates in the formation of acetyl CoA, the further oxidation of which is a pathway common with carbohydrate metabolism, fatty acid oxidation, too, leads to oxidative phosphorylation.

Of the individual oxidative reaction steps in the cycle, that of succinate to fumarate is carried out by direct coupling between succinic dehydrogenase and the respiratory enzyme chain, but the other substrate oxidations, those of pyruvate, citrate, ketoglutarate, and malate, take place via DPN and TPN None of the oxidative reactions between intermediates and DPN or TPN leads to the phosphorylation (except for the ketoglutaric-succinic step, as explained above), but the oxidation of DPN or TPN by the respiratory enzyme chain leads to the formation of three high-energy phosphates per mole of coenzyme oxidized, or per atom of oxygen utilized One of these steps seems to be related to the coenzyme oxidation directly, which step is lacking in the oxidation of succinate. The two other phosphorylations must be linked with events in the cytochrome series By counting up all the phosphorylation steps involved in the complete oxidation of a mole of glucose, one comes to a yield of 36 to 40 moles of high-energy phosphate Comparison of this with the 2 moles obtained by glycolysis clearly reveals how much more exhaustive utilization of foods is obtained with the respiratory process.

It is obvious that, without respiration, no phosphorylation takes place, but the opposite can likewise be true, since the phosphorylative steps are obligatory parts of the total reaction This coupling, however, can be broken by various substances, in which case oxidation can proceed freely. In vivo, the rate of respiration must be determined by the rate of processes utilizing high-energy phosphates, which provide phosphate acceptors for the respiratory process, unless there are physiologic uncoupling agents, or alternate mechanisms of energy conservation and transfer.

The mechanism by which phosphate radicals are incorporated by the reactions of the respiratory enzymes is not at all known, but is the subject of penetrating investigations One important aspect is that the entire complex of respiratory reactions takes place in an organized structure, located in the *mitochondria* or *sarcosomes* It must be pointed out that the oxidatively active types of muscle, such as the myocardium, are well provided with sarcosomes, which are situated in close proximity to the contractile fibrils

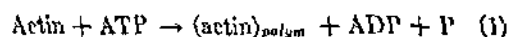
THE MOLECULAR PHYSIOLOGY OF CONTRACTION

Present knowledge of the molecular mechanisms operative in contractile activity is almost entirely based upon investigations on the structure of the proteins actin and myosin, and their interaction with ATP. During the early developments in this field, only one protein, then named *myosin*, was recognized The investigations of Weber (1934) and von Muralt and Edsall (1930) comprise the main efforts during this period. A new epoch set in with the discovery of the enzymatic activity of myosin as an ATPase (Engelhardt) and of certain physical changes undergone by *myosin-ATPase* during its activity (Dainty et al., 1944). These investigations indicated that the structure protein of the muscle fibril catalyzes the energy-yielding reaction, and undergoes a physical modification (possibly representing the basis of contraction) in the course of doing so Detailed progress, however, depended on a series of investigations by Szent-Gyorgyi and his collaborators, which is still in progress.

The protein which is obtained by prolonged extraction of minced muscle with 0 5 *M* buffered potassium chloride, and which earlier was called "myosin," is in reality a complex of two separate well-defined proteins, *myosin* and *actin* The former constitutes about half the total muscle protein and is the only fibrillar protein with ATPase activity It was crystallized by Szent-Gyorgyi (1943) and was later obtained in entirely pure and undenatured condition It appears to consist of rod-shaped mole-

cules with a length of 0.16 μ and with a molecular weight of 420,000 By means of controlled tryptic digestion, myosin can be decomposed into a *light* and a *heavy meromyosin*, of which the latter retains the ATPase activity and the property of combining with actin Each of these components consists of further subunits, called protomyosins

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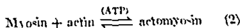


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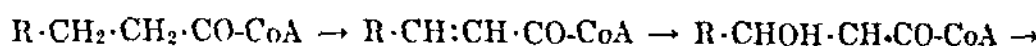
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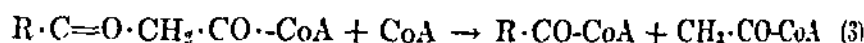
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The mechanism by which phosphate radicals are incorporated by the reactions of the respiratory enzymes is not at all known, but is the subject of penetrating investigations. One important aspect is that the entire complex of respiratory reactions takes place in an organized structure, located in the *mitochondria* or *sarcosomes*. It must be pointed out that the oxidatively active types of muscle, such as the myocardium, are well provided with sarcosomes, which are situated in close proximity to the contractile fibrils.

THE MOLECULAR PHYSIOLOGY OF CONTRACTION

Present knowledge of the molecular mechanisms operative in contractile activity is almost entirely based upon investigations on the structure of the proteins actin and myosin, and their interaction with ATP. During the early developments in this field, only one protein, then named *myosin*, was recognized. The investigations of Weber (1934) and von Muralt and Edsall (1930) comprise the main efforts during this period. A new epoch set in with the discovery of the enzymatic activity of myosin as an ATPase (Engelhardt) and of certain physical changes undergone by *myosin-ATPase* during its activity (Dainty et al., 1944). These investigations indicated that the structure protein of the muscle fibril catalyzes the energy-yielding reaction, and undergoes a physical modification (possibly representing the basis of contraction) in the course of doing so. Detailed progress, however, depended on a series of investigations by Szent-Györgyi and his collaborators, which is still in progress.

The protein which is obtained by prolonged extraction of minced muscle with 0.5 *M* buffered potassium chloride, and which earlier was called "myosin," is in reality a complex of two separate well-defined proteins, *myosin* and *actin*. The former constitutes about half the total muscle protein and is the only fibrillar protein with ATPase activity. It was crystallized by Szent-Györgyi (1943) and was later obtained in entirely pure and undenatured condition. It appears to consist of rod-shaped mole-

2

Metabolism of the heart

W. F. H. M. MOMMAERTS

Among studies on the metabolism of the heart, one must distinguish between those of the chemical processes in the myocardium, related to the performance of work, and those related to the initiation, conduction, and regulation of automatic activity, or to the regulation of coronary flow. Investigations in the latter areas have not yet led to any coherent knowledge, although isolated inquiries have been made (Davies et al, 1952, Mommaerts et al, 1953, Alella, 1954, 1955) The metabolism and mechanical performance of the myocardium have obvious similarities to those of skeletal muscle, and much of the content of the previous chapter is immediately applicable to the heart It remains to discuss those aspects of cardiac metabolism which are characteristic for this organ in situ, and which explain its ability to perform uninterrupted work without fatigue It will be left to separate chapters (Chaps 3 and 9) to describe the regulation of cardiac output and of the metabolic adjustments connected with it

PHYSIOLOGIC ORGANIZATION OF THE ENERGY METABOLISM OF MUSCLE

There are two ways in which the metabolism

former mode of breakdown, 1 mole of glucose yields 2 moles of high-energy phosphate, in the latter, eighteen or twenty times as much This section considers how, in various examples of muscular tissues, one or the other type of metabolism predominates These considerations are based upon the classical investigations of Hill (1926, 1927, 1931) and Meyerhof (1930), and upon quantitative relations derived elsewhere (Mommaerts, 1950).

The resting metabolism of skeletal muscles is usually at a very low level of intensity, corresponding to a breakdown and equivalent regeneration of ATP ranging from about 0.1 μm/Gm/min (frog muscle at room temperature) to about 1μm/Gm/min (mammalian muscle at body temperature in tonic rest). These low turnover rates are easily covered by low rates of respiration, which can be maintained even when only a small part of the capillary circulation is patent. The mammalian heart, artificially arrested, has a higher rate of metabolism, not as a sign of wastefulness, but because the resting state has no place in the function of this organ

In activity, metabolic intensity increases enormously, apparently no less than a thousandfold for frog muscle and several hundredfold for human exercise. The rise in metabolism in extreme cardiac activity is less, partly because the resting value is higher, partly because of a more favorable economy (if that term can be used for an intermittently contracting muscle). The question arises whether respiration in various muscles can be sufficiently enhanced to accommodate these increased energetic demands The answer is that often it cannot

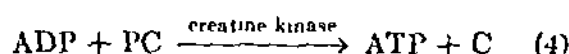
This may be illustrated, for example, by the course of heat production related to the activity of a frog muscle (Hartree and Hill, 1922). This consists of heat produced during the activity (initial heat in case of a twitch, maintenance heat during a tetanus), followed by the

which may permit a closer study, on the subvital level, of the interrelations between respiration, phosphorylation, and contractile activity. Contractile fiber bundles have also been prepared from the heart, which display activities generally similar to those of skeletal muscle. The extensive studies of Weber have led to the viewpoint that contraction is directly caused by the hydrolytic splitting of ATP, the mere presence of this substance having the effect of plasticizing the fiber to provide facilitated mobility of its constituents.

Addition of certain muscle proteins (the so-called relaxation factor) to a glycerol-extracted muscle preparation leads to a system in which alternate contraction and relaxation can be evoked by relatively small changes in pH (Goodall and Szent-Györgyi, 1953, Lorand, 1953) or bivalent cations (Bendall, 1953, Bozler, 1953). These relaxation-factor preparations contain *myokinase*, *creatine kinase*, or other enzymes, and the relaxation phenomenon seems correlated with a partial resynthesis of the ATP broken down during its interaction with the contractile matter·



$$2\ \text{ADP} \xrightarrow{\text{myokinase}} \text{ATP} + \text{AMP} \qquad (3)$$



$$\text{ADP} + \text{PC} \xrightarrow{\text{creatine kinase}} \text{ATP} + \text{C} \qquad (4)$$

There are some difficulties against this view in its simplest form, and a completely different picture may well arise from the discovery by Kumagai et al. (1955) that, in addition to the above enzymes which prolong the lifetime of the added ATP, a more specific protein is needed.

Knowledge of the intricate structure of the contractile machinery of muscle has been advanced greatly by the application of electron microscopy, and some studies on muscle have achieved a high standard of perfection From selective extraction experiments, checked by electron optical and phase-contrast observations, Hanson and Huxley conclude that myosin occurs in the form of heavy rods throughout the length of the A band, while thinner actin filaments extend from the Z membrane throughout the I band into the A band to the limit of the H zone. Contraction of glycerol-extracted muscle fibers consists of a migration of the actin filaments into the H zone. In strong contraction, material may even accumulate in the H zone and cause the appearance of contraction bands. Stretching, on the other hand, causes a movement of actin filaments out of the A band. It is possible, of course, that further technical advances may lead to some modification of this picture.

Most recent investigations on the mechanism of contractility have been performed on extracted tissues or with isolated components It will still be necessary to demonstrate the applicability of these phenomena to living muscle It will be necessary to demonstrate experimentally whether ATP breakdown is intimately related to the activity of living muscle and to investigate the temporal and quantitative connection between these phenomena

To a limited extent, these questions can be approached by optical methods applied to living tissue. But, in order to investigate the occurrence of any reaction, it is necessary to interrupt a muscle during contraction and to subject it to analysis in comparison with a control muscle. In tetanic activity, whether elicited pharmacologically or by stimulation, a breakdown of high-energy phosphates can be shown to occur, although the selective diminution of ATP in some cases, of PC in other cases, remains to be explained. However, after a brief tetanus of frog muscle at low temperature, a degree of activation only barely exceeding that in a single twitch, none of the expected changes could be detected.

For a truly penetrating investigation of this problem, it would be required to interrupt instantaneously a muscle during the course of a single contraction. This has been accomplished (Mommaerts and Schilling, 1955) by high-speed immersion of a pair of muscles (one of which is stimulated) into liquid propane or isopentane cooled to −185°C. This procedure effects immediate stopping of the muscle at any stage of a single twitch Muscles treated in this fashion do not show a breakdown of ATP or of PC at any point of the contraction or relaxation cycle (Mommaerts, 1954, 1955; Fleckenstein et al., 1954).

Further work is required to evaluate the impact of this negative result The possibility exists that unknown phosphagens occur in muscle which, by a rapid process of phosphate transfer, conceal the breakdown of ATP that might have taken place. It would be useless to discuss the situation until that question has been decided.

pathway of carbohydrate metabolism However, the human heart does not use glucose exclusively, and it is obvious that adaptation for persistent work includes a variety of factors besides those directed toward oxygen uptake

CARDIAC METABOLISM IN SITU

As with skeletal muscle, the metabolism of the heart depends on its activity When the performance of work increases, the rate of metabolism rises and its energetic efficiency becomes improved to an optimal value of about 25 per cent (Bing et al , 1949), above which it declines again at overoptimal loads However, with regard to the oxygen extraction from the perfusing blood, the heart differs from other muscle or other organs. Average peripheral tissues extract about one-third of the oxygen brought by the blood, so that the pooled venous effluent still carries some 13 or 14 per cent of this gas With the sigmoid shape of the dissociation curve, this means that under conditions of increased demand, the oxygen extraction can be about doubled with only a small lowering of the remaining oxygen tension *The myocardial extraction, however, is more complete*, and leaves only *4 to 7 per cent* oxygen in the coronary blood Any further utilization would lead to an undesirable drop in oxygen tension, so that all conditions of increased demand are accompanied by an enhanced coronary flow, leaving the oxygen extraction unchanged (Lombardo et al , 1953) It has already been pointed out that during periods of transition toward a greater coronary circulation, myoglobin protects the heart against a passing hypoxic condition

The heart can contract only a small oxygen debt, and it seems to avoid that situation. The respiration of the left ventricle in normal human subjects is of the order of 8 ml oxygen/100 Gm/min, derived from about 65 ml blood during the same interval (Bing et al , 1949) In congestive failure, the respiratory activity of the heart is unchanged, so that its reduced work output implies a decreased energetic efficiency

The problem of the specific substrates used for combustion has frequently been studied with purified enzymes, with homogenates or mitochondrial suspensions, and with tissue slices Important as these studies have been to discover the possible pathways of metabolism, they give no information as to the preference of the intact heart toward individual nutrients. More physiologically, the problem has been studied on intact surviving hearts in the heart-lung preparations, or with techniques for entirely isolated perfusion (Lorber, 1953). Such investigations form a valuable background of information, and have shown that glucose, lactate, pyruvate, and fatty acids are suitable as substrates (Evans, 1936). Still, the isolated heart misses the physiologic regulations of the intact body, and it often shows a rather low efficiency and a progressive hypodynamicity. Recently, Goodale, Bing, and their associates have developed catheterization techniques for the sampling of blood from the coronary sinus, with which the extraction and utilization of individual substrates can be investigated. Some of the main results of these efforts will be presented; for more extensive reviews see Olson and Schwartz (1951) and Bing (1955, 1956).

By simultaneous measurement of the coronary blood flow by nitrous oxide saturation or desaturation techniques (Goodale and Hackel, 1953, *Bing et al* , 1949) and of the extraction of individual substrates, one can determine the share of each substrate toward the total oxygen consumption, as well as the dependence of its *utilization* upon the arterial concentration

Glucose is found to be extracted only above a rather high threshold value of about 60 mg/100 ml Between this value and a limit of about 100 mg/100 ml, the glucose uptake increases to a maximum and then remains about constant, provided that the organism *is in* a steady state of carbohydrate metabolism (Goodale et al , 1948, 1950, Bing et al , 1953). *Lactate* and *pyruvate* are likewise absorbed above threshold concentrations of about 1.6 and 0.4 mg/100 ml, respectively. In human subjects after a meal, Goodale et al (1948, 1950) found that these combined carbohydrate sources could account for nearly the whole of the oxygen consumption of the heart, but inasmuch as some carbohydrate may have been deposited, this does not exclude the use of other nutrients This was indeed found by Bing (1955), whose results (Table 2-1), in good agreement with the general trend of observations on the isolated heart, show that only about *one-third* of the myocardial metabolism is due to carbohydrates Among these, glucose and lactate are consumed about equally, not-

delayed or recovery heat, which may last for many minutes. The latter accurately coincides with the extra oxygen consumption (D. K. Hill, 1940a, b). Even if admittedly some of this extra respiration could take place during the activity period, as it will in a sufficiently prolonged tetanus, it is still obvious that the greater part occurs during the delayed period. This is expressed by stating that the active muscle engages an *oxygen debt*. For the total human body in intense exercise for half a minute (e.g., in a 200-m dash), only about one-fifth of the increased respiration takes place during the period of activity, the remainder constitutes the oxygen debt. The additional energy-yielding processes during the activity itself are glycolysis on the one hand, fargoing depletion of the high-energy phosphate reserves on the other hand. These reactions are then reversed during the restitution period. Resynthesis of ATP and PC must take place within the muscle itself, by the processes involved in oxidative phosphorylation. Oxidative resynthesis of glycogen from lactate can also take place within the muscle, as it does in isolated muscles. This process seems to be rather slow, perhaps because it is limited by the *Utter reaction* (Part 2, Chap. 1), which may not be well developed in all muscles. However that may be, most of the lactic acid in the intact mammalian body is carried away by the blood stream to the liver. It is here that the resynthesis of glycogen takes place, whereupon carbohydrate is gradually returned to the muscles as blood glucose, from which muscle glycogen can be formed directly in the presence of ATP.

It is obvious that the arrangements based upon the oxygen debt, whereby a much greater power[1] can be exerted than the capacity of the oxidative enzymes permits, can be used only for limited intervals of time. Characteristically, therefore, this mechanism is used by muscles designed to carry out short periods of intense activity. In the typical case, these are *white muscles* (Needham, 1926), so called because they do not contain myoglobin. Even these muscles can perform steady work over long periods, but must do so at a rate sufficiently low to permit a steady regeneration of ATP by their oxidative enzymes. Most muscles in the human body are of an *intermediate, or mixed, type*, but can be grouped with white muscle in this qualitative discussion, because they are not able to maintain a steady state of oxidative phosphorylation at the level of their more intense activity.

[1] The word power is used here in a strictly physical sense, meaning energy output per unit of time.

If persistent activity at a high level is needed, the muscle has to possess a much more pronounced development of its *oxidative phosphorylative enzyme systems*, including the cytochromes and their oxidase and the enzymes of the citric acid cycle and its feeder reactions. Such muscles are encountered in a variety of wild animals, e.g., in the pectoral muscles of long-flying birds. Universally, the myocardium is such a muscle, since it is active without interruption. Since the oxidative enzymes occur in an organized state in the *mitochondria* or *sarcosomes*, it will be understood that these bodies are numerous in these types of muscles, including the heart (Paul and Sperling, 1952).

A second visible feature of such muscles is that they are usually provided with myoglobin (Millikan, 1939). This is a pigment related to hemoglobin, which reversibly binds oxygen (Theorell, 1934). Its affinity to oxygen is so great that at the oxygen tension usually prevalent in the tissues, it does not become dissociated, but remains combined to form an intracellular oxygen reserve. The functional meaning of this is not clear in all cases, but can perhaps be understood, for the heart, as follows: the myoglobin-bound oxygen suffices to provide for the respiration of several contraction cycles. This is not normally utilized, but is called upon during the first few seconds before the coronary circulation has adjusted itself to the new requirements (Gregg, 1950) when the heart is suddenly brought to a higher level of activity.

It is not sufficient for a contractile tissue to have a sufficient implement of oxidative enzymes, but it must also be richly vascularized because of the requirements for transporting respiratory gases as well as nutrients. A typical *white muscle*, working under the conditions of oxygen debt, may well engage in a *metabolite debt* at the same time, by exhaustive use of its glycogen store. A steadily working organ, on the other hand, cannot rely upon stored fuel, but must be in a stationary state of supply in this regard too. If a *red muscle* were intensely using blood glucose, it would have to have sufficient hexokinase to be able to draw it into the

pathway of carbohydrate metabolism. However, the human heart does not use glucose exclusively, and it is obvious that adaptation for persistent work includes a variety of factors besides those directed toward oxygen uptake

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TABLE 2-1 RELATIVE CONTRIBUTION OF CARBOHYDRATES AND NONCARBOHYDRATES TO TOTAL MYOCARDIAL OXYGEN USAGE

Carbohydrate, %		*Noncarbohydrate, %*	
Glucose	17 90	Fatty acids	67.0
Pyruvate	0 54	Amino acids	5 6
Lactate	16 46	Ketones	4 3
Total	34 90	Total	76 9

SOURCE: From Bing (1955)

withstanding the lower blood level of the latter, showing that lactate is a preferred substrate In proportion to the blood levels, pyruvate is utilized less than lactate Since both substances are metabolized by the same pathway of oxidation, this difference may reflect a difference in permeability The bulk of the remaining fuel is accounted for by fatty acids. The actual proportions between individual nutrients will depend on the diet and the nutritional status, a diet of fat, for example, will raise the proportion of fatty acid oxidation.

It will be observed that the sum of the different nutrients in Table 2-1 accounts for more than 100 per cent of the simultaneously measured oxygen consumption Obviously, the substrates are not completely oxidized but are to some extent stored under the conditions of the measurements, which were made postprandially The technique of catheter sampling does not as yet permit decision as to which substances are stored, but this can be grossly inferred under conditions of increased supply When glucose is suddenly administered it is extracted at an enhanced rate, the upper threshold being no longer in evidence A raised fatty acid level causes an extra uptake in excess of the total oxygen consumption, and already a small rise in the blood level of the amino acids causes a large increase in their uptake, which can account for 40 per cent of the cardiac respiration (Bing et al , 1954) All these changes are indicative of storage in the heart

It has already been pointed out in Chap 1 that the combustion of *fatty acids* proceeds by beta oxidation of their coenzyme A derivatives with the formation of acetyl coenzyme A, as in the oxidation of carbohydrates. *Ketone bodies* are likewise oxidized by similar pathways, and this process is increased somewhat in diabetes *Amino acids* too, after preliminary changes of greater or lesser complexity, give rise to intermediates encountered in carbohydrate or fat oxidation, or to members of the citric acid cycle. All major fuels have, therefore, a final common pathway of oxidation, and these reactions are all coupled with phosphorylative steps. The final purpose of metabolism, the generation of high-energy phosphate compounds, can thus be accomplished in a great many different ways, and this metabolic versatility of the heart may well assure its proper function under a variety of conditions.

The oxidation of amino acids seems to be of minor significance under most circumstances and is held to play no role in the isolated heart. However, the above-mentioned results of Bing might not be entirely attributable to amino acid storage. If the ammonia liberated in an oxidative process does not escape as such, it might appear in the form of glutamine The high glutamine content of the heart, the highest in the body (Archibald, 1945), would warrant an inquiry into the nitrogen metabolism of this organ. Alternatively, the amino acids might be deposited as protein, and the turnover of individual protein fractions of the heart in various conditions would likewise constitute a profitable field of study.

PATHOLOGIC DISTURBANCES IN CARDIAC METABOLISM

It will not be attempted to give a detailed account of the manifold metabolic alterations of myocardial metabolism in various disorders This can more profitably be done in connection with specific diseases However, a general discussion may serve to facilitate the classification of cardiac metabolic disturbances.

DISTURBANCES IN MYOCARDIAL METABOLISM

1 Disturbances in energy production with reduced cardiac efficiency
   a Beriberi heart disease
   b Myocardial ischemia and hypoxia (hemorrhagic shock, coronary occlusion, ventricular fibrillation, hypothermia)
2 Disturbances in energy production without decreased cardiac efficiency
   a Diabetes
3 Disturbances in energy utilization with reduced cardiac efficiency
   a Congestive failure

SOURCE From Bing (1955)

Leaving out diabetes, in which the metabolic characteristics are altered while the generation of energy does not seem directly impaired

(Ungar et al., 1955), a reduced cardiac performance may be ascribed to either *decreased production or disturbed utilization of metabolic energy* (Olson and Schwartz, 1951). As an example of the former, one may cite thiamine deficiency leading to beriberi heart disease, because in it the primary biochemical lesion is easily recognizable, viz., a lack of thiamine pyrophosphate, which has already been described as a crucial coenzyme in the catabolism of pyruvate and of α-keto acids in general. Disturbances in the cardiac utilization of pyruvate and lactate, and other metabolic defects, are indeed referable to a lack of this coenzyme (Hackel et al., 1953). Since with a normal supply of thiamine, the maintenance of its pyrophosphate depends on a sufficient supply of ATP, the question also arises whether the reduced energy provision following hemorrhagic shock or coronary occlusion, or in ventricular fibrillation, might not be due to a depletion of cocarboxylase (*Govier and Greer, 1941*). *It* has been shown that, in fibrillation, the ATP level falls progressively *(Paul et al., 1954)*. However, other coenzymes might be reduced too, and it remains to be investigated from case to case which coenzyme depletion is the most critical, e.g., thiamine pyrophosphate is not destroyed after coronary artery ligation while DPN is (Govier, 1945).

A disturbance in energy utilization, in contrast to energy production, *is assumed to be the cause of congestive failure*. This conclusion rests primarily upon the demonstration *that* progressive hypodynamism of the isolated heart consists of a diminished performance at constant oxygen consumption (Starling and Visscher, 1927, Lorber, 1953). Since it is questionable whether the acute deterioration of the isolated heart, although responsive to cardiac glycosides, is fully comparable to the chronically hypodynamic state in congestive failure, it is significant that the same reduction in efficiency has also been demonstrated for the failing human heart in vivo (Blain et al., 1955). There is a difference in that the human heart has an unchanged respiration with a greater diastolic fiber length, but it would require a deeper insight to judge whether this difference is essential or not. The reduced performance with unchanged respiration might also be due to an uncoupling of oxidation and phosphorylation, such as can be brought about by dinitrophenol. In this case, one would expect the content of high-energy phosphates to be drastically lowered. This does not seem to be the case (Wollenberger, 1947; Fawaz and Hawa, 1953) in the isolated heart, therefore, it is the utilization of these compounds, not their generation, which is at fault. One thinks of this in terms of a disturbance in the processes which constitute the interaction between energy donors and the actomyosin of the contractile fibrils. Since it is this type of disturbance which is corrected by cardiac glycosides (Wollen*berger, 1949*), numerous efforts have been made to show that one property or another of myosin, actin, or actomyosin is modified by drugs of this class. Some of these results are quite credible, yet the over-all impression is that this direct mechanism of action is not convincingly demonstrated. Rather, one would assume that the cardiac glycosides, and possibly certain physiologic regulators (Titus, *Weiss*, and Hajdu, 1956) act by means of processes similar to those brought into the discussion on the mechanism of the staircase effect (Hajdu, 1953; Szent-Gyorgyi, 1953).

3

Hemodynamic determinants of myocardial oxygen consumption

STANLEY J. SARNOFF AND EUGENE BRAUNWALD

A precise appreciation of the hemodynamic determinants of the consumption of oxygen by the heart is of fundamental importance to the understanding of both basic cardiac physiology and clinical heart disease There have been essentially three main points of view concerning this matter (1) that the primary determinant of the oxygen consumption by the heart is the amount of external work it performs (pressure × flow) (Barcroft and Dixon), (2) that although any increase in work requires an increase in oxygen consumption, this increase will be greater when the work is augmented by elevating aortic pressure than when work is increased by augmenting cardiac output (Evans and Matsuoka), (3) that the oxygen consumption of the heart is determined by ventricular end-diastolic fiber length (Starling and Visscher) The third is perhaps the most generally accepted view.

EXPERIMENTAL OBSERVATIONS

In an attempt to gain further insight into this problem, a special metabolically supported, isolated heart preparation was devised In this preparation, when stability is achieved, it is possible independently to control aortic pressure, heart rate, and cardiac output while measuring oxygen consumption with a high degree of precision (Fig. 2-3), and the performance characteristics (Sarnoff et al , 1958) are nonfailing and comparable to those of the heart in situ

In this preparation, when left ventricular work is increased by elevating aortic pressure while keeping stroke volume and heart rate constant (a pressure run), the myocardial oxygen consumption parallels the work while external myocardial efficiency (work divided by oxygen consumption) remains unchanged (Fig 2-4, *P.R*). In contrast, when work is increased by augmenting cardiac output with mean aortic pressure and heart rate held constant (a flow run), only a slight increase in the oxygen consumption of the heart occurs and efficiency rises markedly (Fig 2-4, *F.R.*). It is of interest that with an augmented stroke volume, the slight increase in oxygen consumption that does occur is accompanied by an increase in both the systolic pressure and the duration of ventricular systole It was further observed that an increase in minute oxygen consumption and a decrease in myocardial efficiency occur when the heart rate is increased while mean aortic pressure and cardiac output are constant (Fig 2-5C). This is accompanied by an increase in the total duration of ventricular systole per minute.

Further data were then obtained to ascertain whether the results shown in Fig 2-4 are limited to a narrow hemodynamic range or apply to wide ranges of pressures and flows. These results are shown in Fig. 2-5. Figure 2-5A shows representative results from that type of experiment in which data from three successive pressure runs were obtained at each of three different cardiac output levels. It will be observed that when aortic pressure alone is

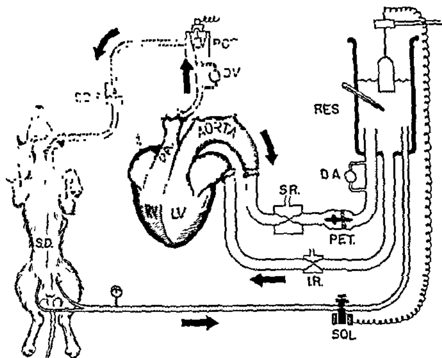


Fig 2-3. Schematic diagram of the isolated supported heart preparation. *S R*, Air-filled Starling resistance; *PET.*, Potter electroturbinometer, *D A*, arterial densitometer, *RES*, reservoir; *I R*, water-filled inflow Starling resistance; *D.V*, venous densitometer, *ROT.*, rotameter; *S D.R.*, support dog reservoir, *S D*, support dog; SOL, solenoid valve electrically operated by microswitch at top of reservoir float. For further details see Sarnoff et al., 1958.

P.R. F.R.

A.P. mm. Hg 200 100 0

S.V. c.c. 30 20 10 0

C.O. L/min. 5.0 3.0 1.0

O_2 cons. c.c. per min. 20 10 0

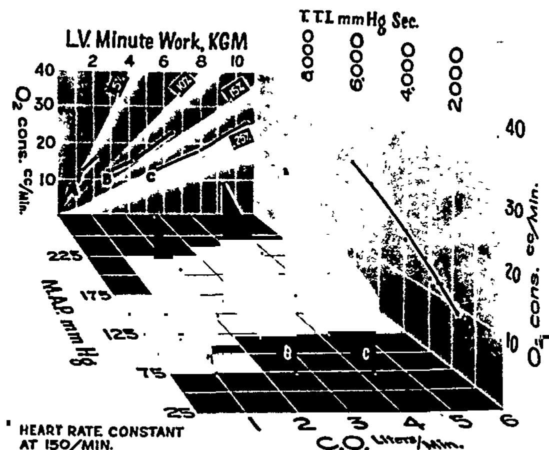
Eff. % 10 0

HR=138

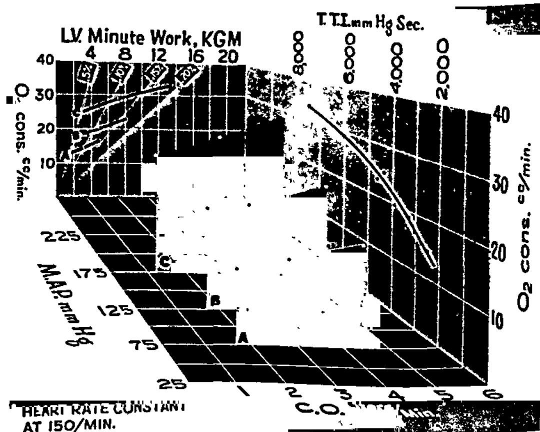
1.0 2.0 3.0 0 1.0 2.0 3.0 4.0 5.0

LEFT VENTRICULAR MINUTE WORK KGM

Fig 2-4 Contrasting effects on myocardial oxygen consumption of increasing work by increasing mean aortic pressure ...



A



B

(Legend on facing page.)

increased, the above-described *parallel* relationship between ventricular work and myocardial oxygen consumption obtains over the entire range of cardiac outputs examined. Results from that type of experiment in which data from three successive flow runs were obtained at each of three different mean aortic pressure levels are shown in Fig. 2-5B It will be noted that the above-described *nonparallel* relationship between ventricular work and myocardial oxygen consumption, when cardiac output alone is increased, obtains over the entire range of mean aortic pressures examined. That is, the increase in oxygen consumption is small relative to the large increments in ventricular work which occur.

The influence of heart rate is seen in Fig. 2-5C. With mean aortic pressure held constant at 120 mm Hg, and the heart rate at 120/min, cardiac output was progressively increased from 1 2 to 4 9 liters/min. This was then repeated at heart rates of 160/min and again at 200/min. It will be observed that at any given mean aortic pressure and cardiac output, a higher heart rate is accompanied by an increased myocardial oxygen consumption, and external myocardial efficiency is thereby decreased

The above experiments strongly suggested

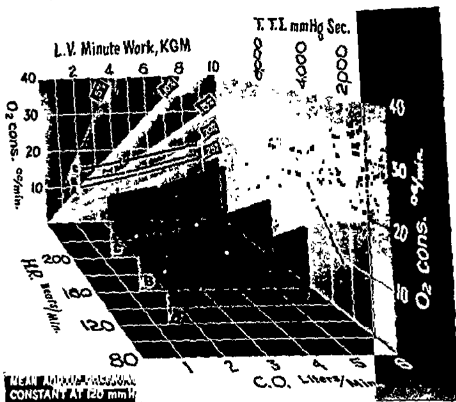


Fig. 2-5 The base panel shows the experimental conditions (cardiac output, aortic pressure, heart rate) when each determination of oxygen consumption was made. The height above the base panel of each experimental point represents the oxygen consumption. The rear panel shows the plot of left ventricular minute work in kilogram meters against myocardial oxygen consumption The shaded lines on the rear panel labeled with per cent figures are iso-efficiency (external) lines The right hand panel shows the relationship between the tension-time index (T T I.) in millimeters of mercury seconds and myocardial oxygen consumption in cubic centimeters per minute A Three pressure runs at low, medium, and high cardiac outputs Note the negligible change in external efficiency as aortic pressure is increased within any given run B. Three flow runs at low, medium, and high mean aortic pressures Note the increase in external efficiency within the course of any given flow run C. Three flow runs at heart rates of 120, 160, and 200/min Note the increased oxygen consumption at any given level of left ventricular work at the higher heart rates. (From Am J. Physiol., 1958)

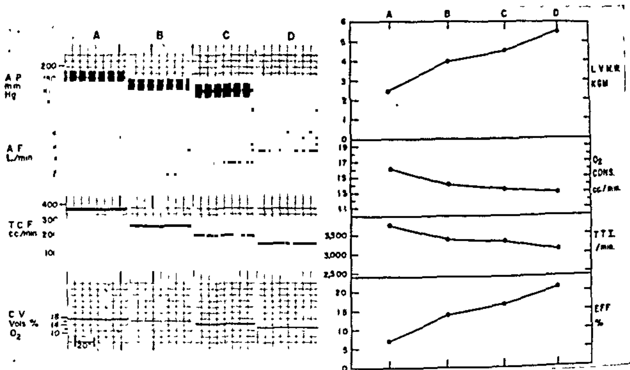


Fig. 2·6 Experiment which shows an increase in left ventricular minute work, *L.V.M.W.*, accompanied by a decrease in myocardial oxygen consumption. Note parallelism between myocardial oxygen consumption and the tension-time index (*T.T.I.*). *A F.*, Aortic flow; *T.C.F.*, coronary flow. Sum of *A.F.* + *T.C F.* = cardiac output. *C.V.*, Coronary sinus blood oxygen content in volumes per cent as determined by intraexperimentally calibrated densitometer. (*From Am. J. Physiol.*, 1958.)

that myocardial oxygen consumption bears little relation to the external work per se of the heart. The absence of such an interrelationship is even more convincingly demonstrated by the experiment shown in Fig 2-6 Left ventricular minute work was progressively increased by augmenting cardiac output while lowering aortic pressure to a lesser extent at a constant heart rate. A 128 per cent increase in work was accompanied by a 20 per cent decrease in oxygen consumption

From the foregoing data it was postulated that *myocardial oxygen consumption is determined by the total tension developed by the myocardium* in so far as this is reflected by the total area beneath the systolic portion of the pressure pulse. The term "tension-time index" (T.T I.) refers to this parameter, which is calculated as the product of the mean systolic pressure, the duration of systole, and the heart rate.

An attempt was made to correlate myocardial oxygen consumption with each of the pertinent hemodynamic parameters, viz (1) mean, mean systolic and peak systolic aortic pressures × heart rate, (2) left ventricular work, (3) cardiac output, (4) left ventricular filling pressure (Fig. 2-7), (5) duration of ventricular systole, (6) heart rate, and (7) the T.T I It was observed that the only consistent correlation was between myocardial oxygen consumption and the T.T.I., as is apparent in Figs. 2-5 and 2-6. *It appears, therefore, that in any given functional state of the heart, the T.T I (mean systolic pressure times duration of systole times heart rate) is the principal, if not the sole, determinant of myocardial oxygen utilization.* If these correlations are causal rather than coincidental, then the above data provide a more meaningful relationship between the oxygen used by contracting heart muscle and the physiologic purpose for which the oxygen is used.

At any given filling pressure, the myocardial oxygen consumption can vary over a substantial range (Fig 2-7) and will be a function of the T T I. developed during the course of the contraction It appears, therefore, that the oxygen consumption of the heart is influenced not alone by the filling pressure prior to contraction, but also by the events occurring subsequent to the onset of contraction from any given filling pressure. If marked changes in ventricular distensibility do not occur, this view implies

that similar considerations also apply to the relationship between fiber length and myocardial oxygen consumption

The above-described hemodynamic determinants of myocardial oxygen consumption were found to apply in the dog with a complete circulation as well. It was also noted that the same hemodynamic factors which influence myocardial oxygen consumption influence coronary flow in a similar fashion That is, when work was increased by elevating aortic pressure, coronary flow increased to a much greater extent than when work was increased by augmenting cardiac output. The dependence of both myocardial oxygen consumption and coronary blood flow on the same hemodynamic parameters suggests an interdependence between them and provides further evidence in support of the view that the primary determinant of coronary flow is the requirement of the heart for oxygen (Gregg, 1950)

CLINICAL CONSIDERATIONS

An extension of these findings to the diseased state in man may provide a more precise appreciation of the interrelationship between the oxygen requirement of the heart and the deviations from normal produced by various pathologic conditions. Thus, the overt manifestations

is substantially elevated. Such manifestations are infrequently brought about by conditions like mitral insufficiency, intra- and extracardiac shunts, and beriberi heart disease, in which cardiac work is increased because of an increased cardiac output and in which the elevation of T.T.I. is only slight However, in the presence of coronary artery disease, the influence of the oxygen requirement of the heart, which normally regulates coronary vascular re-

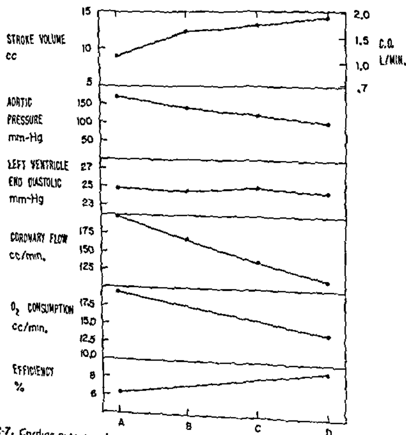


Fig 2-7. Cardiac output and aortic pressure were reciprocally varied in such a manner as to hold left ventricular end-diastolic pressure constant. Note change in oxygen consumption.

sistance and flow, is largely obviated by the change in the locus of the critical resistance element from the adjustable arteriole to an artery with a fixed orifice. When this is the case, coronary flow is determined principally or solely by hydraulic factors, prominent among which is the time available for flow, i.e., *the duration of diastole.* It has been observed that tachycardia, an increase in stroke volume, the presence of a depressed ventricular function curve and/or a descending limb, and markedly elevated systolic pressures, each prolongs the duration of ventricular ejection and thereby reciprocally diminishes the time per minute available for coronary flow.

The extent to which an alteration in any given hemodynamic parameter will favorably or unfavorably influence the relationship between the oxygen requirement of the heart and the delivery of oxygen to it will depend upon the effect of the alteration of that hemodynamic parameter on (1) the T T I. (myocardial oxygen requirement) and (2) hydraulic factors, such as effective coronary perfusion pressure and the duration of diastole (oxygen delivery) These considerations must also be viewed in the light of the influence of any changes in coronary arterial oxygen content due either to anemia or hypoxia

The term *external efficiency* as used here refers to the ratio of external work to oxygen consumption and conforms to the general usage of the term *efficiency* as applied to the heart It is suggested that the term *internal efficiency* refer to the ratio between the *actual total tension* developed by the myocardium and its oxygen consumption External efficiency is primarily meaningful in terms of the relationship between the heart and the total organism but is relatively uninformative about the energetics of contracting myocardium In contrast, the term internal efficiency is designed to expose the meaningful relationship between that aspect of the contraction of the heart which requires oxygen (total developed tension) and the amount of oxygen consumed In the absence of any ready means of measuring the actual total tension developed, the area beneath the systolic portion of the pressure curve (T T I) has been used as an *index* of the actual total myocardial fiber tension. The ratio of T T I. to oxygen consumption thus provides an *internal efficiency index.* Any discrepancy between internal efficiency and the internal efficiency index will revolve around the extent to which mean ventricular radius changes occur and considerations involving *Laplace's law*[1] therefore apply, for it is clear from such considerations that the same intraventricular T.T.I will require a greater myocardial fiber tension in a large heart than in a small one. If it is assumed that the basic relationship is between the total actual tension developed by the myocardium rather than the reflection thereof in the observed T.T.I., then both the low internal and external efficiency of the greatly dilated or failing heart can logically be attributed, at least in part, to the interrelationship between Laplace's law and the dependence of the oxygen consumption of the heart on its actual total developed tension. For example, if the dilated heart is called upon to develop any given intraventricular pressure, the myocardial fiber tension will be greater and its oxygen consumption will thus also be greater than that of the small heart producing the same intraventricular pressure at the same stroke volume and heart rate In this sense, the dilating heart may be thought of as one with an oxygen requirement which approaches or finally could exceed the limit of the oxygen available to it, especially when oxygen availability is limited by disease. It should be emphasized that such considerations are valid only if the assumption of the basic relationship between oxygen consumption and *actual total tension* developed is correct.

Finally, the above observations may also be of interest from the point of view of natural selection Physical stress or conflict is accompanied by large increases in cardiac output in accord with the increased requirements of the organism for oxygen. Under such circumstances, at any given aortic pressure, heart rate, and humoral environment, the oxygen consumption of that organ which delivers greatly increased amounts of oxygen to the whole organism is increased only slightly as a result of increasing stroke volume Thus, it might be that the heart demands a progressively smaller fraction of the total oxygen utilized by the organism as physical activity increases, especially when the heart rate is maintained at low levels as in well-trained athletes

[1] For a cylinder, $T = P \times R$, where T = wall tension, P = intraluminal pressure, R = radius For further discussion see Rushmer's *Cardiac Diagnosis*

4

Origin of the heart beat

BRIAN F. HOFFMAN

The site of origin of the heart beat has been localized to the sinus venosus of amphibians (Gaskell, 1900) and the *sinoatrial* (SA) *node* of mammals (Wybauw, 1910, Lewis et al., 1910–1911; Erlanger, 1913, Eyster and Meek, 1914) Electrical recording techniques employing surface electrodes have shown that an electrical change appears in the region of the pacemaker *prior to the onset* of propagated activity, this potential change appears either as a slow negative variation (Arvanitaki, 1936, Bozler, 1943b) or as an oscillatory change in potential (Rijlant, 1936, Bozler, 1943b, van der Kooi et al., 1956) When, on the other hand, intracellular microelectrodes are employed to record the transmembrane potential of single cardiac fibers, the immediate mechanism responsible for the automaticity of cardiac pacemakers is revealed Although the application of the microelectrode technique to heart muscle has been described in detail (Brooks et al., 1955, Weidmann, 1956), a short summary of this subject will facilitate the presentation of material on cardiac pacemakers

Glass capillary microelectrodes with a tip diameter of less than 1 μ and filled with concentrated potassium chloride can be employed to record the transmembrane potential of single fibers of excitable tissues. When such an electrode is inserted through the membrane of a quiescent fiber, a negative potential of approximately 90 mv is observed This potential difference has been termed *the resting potential* and maintains a steady value in the absence of activity With the onset of excitation, the transmembrane potential rapidly changes from −90 mv to approximately +20 mv, this phase of depolarization and reversal of membrane potential is similar in cardiac fibers from both atrium and ventricle and constitutes the upstroke of the transmembrane *action potential* (Fig. 2-8A). Recovery or repolarization follows a somewhat different course in fibers from atrium and ventricle: in the former, repolarization proceeds at a fairly constant velocity after the end of the upstroke; in the latter, a plateau separates the phases of de- and repolarization. During the plateau, the transmembrane potential is maintained near the zero level (Fig. 2-8). After the end of repolarization, the resting potential of both atrial and ventricular fibers is constant. Although the mechanisms responsible for the action potential of the cardiac fiber are not certain, it is probable that the resting potential depends primarily on a *potassium concentration gradient* across the membrane. Similarly, the upstroke of the action potential is thought to result from a change in membrane permeability and an *inward current of sodium ions* The phase of repolarization may result from another change in permeability which permits an *outward potassium current*

In addition to revealing the true magnitude and voltage-time course of the action potential of the single fiber, the use of intracellular microelectrodes has provided important information on the excitability of heart muscle One of the most important concepts is that of the *threshold potential* If cathodal (depolarizing) stimuli of progressively increasing strength are applied to a single cardiac fiber, it can be seen that for effective stimulation, a depolarization of a certain magnitude must be produced (Fig 2-8B). The level of transmembrane potential

at which depolarization becomes all-or-none in nature has been termed the threshold potential. Any factor which lowers the resting potential to this threshold level will initiate the regenerative depolarization of the action potential upstroke. Information on the refractoriness of the cardiac fiber obtained from microelectrode studies is summarized in subsequent sections

TRANSMEMBRANE POTENTIALS OF PACEMAKERS

In contrast to the description just given for fibers of atrium or ventricle, when records are obtained from *single fibers of pacemakers,* there is no steady resting potential Instead, after the end of the phase of repolarization, the transmembrane potential decreases progressively. When, because of this slow diastolic depolarization, the transmembrane potential attains the threshold level, firing of the pacemaker occurs. The record then shows a smooth transition from slow diastolic depolarization to the rapid depolarization of the action potential upstroke (Fig 2-9A). This pattern of electrical activity was first recorded from pacemaker areas of single fibers in isolated bundles of Purkinje tissue (Draper and Weidmann, 1951). Subsequent studies have shown that the same slow diastolic depolarization is responsible for intrinsic rhythmicity in the sinus venosus (Trautwein and Zink, 1952), the mammalian SA node (West, 1955), and all other cardiac pacemakers from which records of the transmembrane potential have been obtained (Cranefield and Hoffman, 1958).

As can be seen from Fig. 2-9B, C, three major variables influence the time of firing of the pacemaker fiber: one of them is the *slope* of slow diastolic depolarization, and the others are the *level* of the threshold potential and the *magnitude* of the resting potential at the end of the phase of repolarization. An increase in the rate of diastolic depolarization results in an increased heart rate if the other factors remain constant. On the other hand, if the level of the threshold potential changes for a given rate of diastolic depolarization, the time required to reach threshold will be altered and heart rate will vary in the appropriate manner. Finally, with a constant rate of diastolic depolarization and a constant threshold potential, if repolarization is less complete, the threshold level will be reached sooner and cardiac acceleration will result. While a simultaneous change in more than one of these variables is possible, in most instances alterations in heart rate have been found to result primarily from a change either in the slope of diastolic depolarization or in the level of the threshold potential. Specific examples will be mentioned in subsequent sections.

Particularly in the *sinus venosus* or the SA

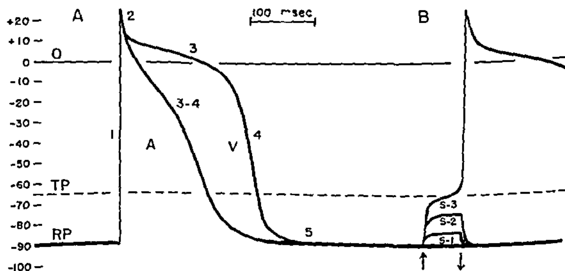


Fig 2-8. A Schematic representation of transmembrane potentials of atrial, *A*, and ventricular, *V*, muscle O, line of zero potential, *TP*, threshold potential, *RP*, resting potential. Numbers refer to different phases of the action potential 1, depolarization; 2, reversal, 3, plateau, 4, repolarization; 5, steady level of resting potential. B Changes in transmembrane potential resulting from two subthreshold rectangular stimuli, *S-1*, *S-2*, and a just-threshold stimulus, *S-3*. See text for discussion.

node, many fibers may show slow diastolic depolarization. Also, under a variety of conditions described below, the site of the pacemaker may shift from one location to another (Eccles and Hoff, 1934; West, 1955). The *true pacemaker* is that area of membrane across which the transmembrane potential first attains the threshold level Other areas of the membrane or other fibers also showing slow diastolic depolarization may be called *latent pacemakers*, they differ from the true pacemaker not only in time of activation, but also because the record of the transmembrane potential shows a sharp inflection, at a level higher than threshold, when the slow depolarization is interrupted by the rapid upstroke of the propagated action potential (Fig. 2-9D) In records obtained from single Purkinje fibers, these criteria are easily met and a clearly localized pacemaker area can be delineated *In the SA node*, on the other hand, it often appears that a number of fibers attain the threshold level almost simultaneously and a single pacemaker fiber firing earlier than others cannot be identified with certainty.

In pacemakers of isolated Purkinje fibers the resting potential (the highest level of transmembrane potential attained after the end of repolarization) does not differ appreciably from that of nonpacemaker fibers (Weidmann, 1955b) In the sinus venosus or the SA node, on the other hand, the resting potential of pacemaker fibers is considerably lower than that of atrial fibers from the same heart Particularly in the mammalian SA node there appears to be a continuous gradation in the magnitude of the resting potential, the values obtained increasing from the center of the node out towards the periphery (West, 1955; Hoffman, 1957). In all *pacemakers the locally* arising action potential shows *a diminished* rising velocity and a decreased or absent reversal As a result, conduction velocity of the pacemaker action potential *is lower than in*

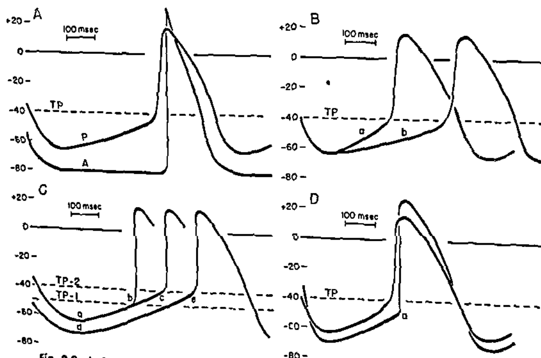


Fig 2-9. A. Transmembrane potentials simultaneously *recorded* from a single fiber in the sino-atrial node, *P, and* atrial muscle, *A*, of the rabbit heart See text for discussion. B. Transmembrane potentials from a pacemaker fiber showing rate change *due to* a change in the slope of slow diastolic *depolarization* from a to b C Transmembrane potentials ... showing changes in rate due ... *of the* resting potential fr... pacemaker *D* Transmem... pacemaker, a ... true pacemaker *fiber* and a latent

unspecialized cardiac fibers. This decreased rate of propagation is particularly prominent in the case of the mammalian SA node. In most instances the change in the action potential upstroke is greater the lower the threshold potential or the level of the membrane potential is at the instant of firing. This relationship is clearly seen in records obtained from Purkinje fiber pacemakers and suggests that the changes in the action potential result from the lowering of the transmembrane potential by slow diastolic depolarization. Weidmann (1955a) has demonstrated a consistent relationship between the level of the transmembrane potential and the rate of rise and amplitude of the action potential, and this, in turn, presumably results from a time- and voltage-dependent sodium-carrying system (Hodgkin and Huxley, 1952; Weidmann, 1955a).

THE CAUSE OF SLOW DIASTOLIC DEPOLARIZATION

Studies of the passive electrical properties of the pacemaker fiber membrane, performed on isolated Purkinje fibers (Weidmann, 1951), have revealed a progressive increase in membrane resistance during the phase of slow depolarization This change suggests a *decrease in ionic permeability*. Moreover, when the concentration of sodium in the extracellular fluid is decreased by replacing sodium chloride with sucrose, the rate of fall of potential diminishes (Draper and Weidmann, 1951). Somewhat similar results have been obtained in studies of SA nodal pacemakers of the rabbit heart (Hoffman, 1957). In addition, numerous studies have indicated that the potassium permeability of the SA pacemaker membrane is lower than that found in nonpacemaker fibers (Cranefield and Hoffman, 1958). These findings suggest that *the slow depolarization of pacemakers may result from a progressive drop in potassium permeability following the end of repolarization* In the presence of a decreasing potassium efflux, the normal inward sodium current would progressively lower the membrane potential until the threshold level had been attained. Clear experimental proof of this mechanism is lacking, however, and the high temperature coefficient of the slope of diastolic depolarization (Q_{10} = 6 0) may implicate some metabolic activity of the pacemaker membrane

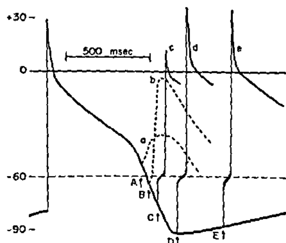


Fig 2-10. Schematic representation of transmembrane action potential of a Purkinje fiber showing some diastolic depolarization Threshold potential shown by dotted line. Stimuli applied early during repolarization, *A*, *B*, elicit only local response, *a*, or slowly rising action potential, *b*, which just succeeds in propagating Somewhat later, *C*, stimulus requirement is less than in the fully recovered fiber, *D*, *E*, demonstrating nature of supernormality See text for discussion.

1 *Role of the refractory period* Records obtained from single cardiac fibers have given a clear picture of the time course of refractoriness in heart muscle By means of electrical stimuli applied to a single fiber, Weidmann (1955a) has shown that the ability of the membrane to respond to a depolarizing stimulus depends primarily upon the degree to which repolarization has occurred Thus, in isolated Purkinje fibers, absolute refractoriness lasts from the upstroke of the action potential until the membrane potential has reached a value of approximately −50 mv Full recovery is not attained until the completion of repolarization (Fig 2-10, *A*) Refractoriness of the membrane to the propagated action potential is similar to that delineated by electrical stimuli (Hoffman et al., 1957). Special effects of anodal stimuli applied during the phase of repolarization have been summarized elsewhere (Cranefield et al , 1957). The action potential of the SA pacemaker fiber is considerably longer in duration than that of the adjacent atrial musculature (Fig 2-10, *a*) As would be expected from this observation, the refractory period of the pacemaker fibers lasts considerably longer than elsewhere in the atrium, this is indicated

by the inability of the pacemaker to follow high atrial rates (Cervoni et al., 1956), as well as by the results obtained on direct stimulation (Hoffman, 1957). *Refractoriness is thus related to the rhythmic discharge of the pacemaker only in so far as it imposes an upper limit on the frequency of the discharge.*

2 *Role of supernormality* A supernormal period has been observed during the recovery of excitability of cardiac muscle (Hoff and Nahum, 1938, Brooks et al., 1955) By means of two intracellular microelectrodes, one used for stimulation and the other for recording, it has been possible to relate this period of enhanced excitability to the change in transmembrane potential during repolarization (Weidmann, 1955a) Near the end of the phase of repolarization, the transmembrane potential is closer to the threshold level than later on during recovery (Fig 2-10, *b*). The stimulus current required to lower the membrane potential to threshold is thus less at this time than after the completion of repolarization and a "supernormal" period is observed Pacemaker fibers of the Purkinje system demonstrate supernormality that is similar to that of nonpacemaker muscle A causative relationship between supernormality and pacemaker activity has not been demonstrated, however, and since the supernormal period ends before the onset of slow diastolic depolarization, the presence of this period of enhanced excitability in pacemakers is not important in production of intrinsic rhythmicity In addition although a possible relationship between supernormality and the production of extrasystoles has often been suggested, there is no convincing evidence in favor of this hypothesis (Cranefield et al 1957 ...

n ...

... In the former case the action potential always has a configuration typical of the SA pacemaker in that the rising velocity is low, the duration is greater than that of atrial fibers, and slow diastolic depolarization is prominent This is true even when the quiescent fiber is driven by applied stimuli In the case of Purkinje fiber, on the other hand, the same area of membrane may change abruptly in so far as the appearance of the action potential is concerned, and a typical pacemaker action potential may be followed on the immediately succeeding beat by a normal action potential with no indication of slow diastolic depolarization.

Records obtained from single fibers of spontaneously beating cultures of embryonic chick heart have shown pacemaker activity similar to that demonstrated in the mature SA node (Fange et al., 1956). In addition, when activity was resumed following a period of quiescence, an oscillatory variation in membrane potential of increasing amplitude preceded the first beat. In cultures obtained from younger embryos, typical slow diastolic depolarization was present in fibers from both atrium and ventricle; in older cultures, on the other hand, the action potentials of ventricular fibers lost this evidence of pacemaker activity.

Records of the transmembrane potentials of single cardiac fibers have provided some new information concerning the pattern of excitation during *arrhythmias* (Cranefield and Hoffman, 1958) These records have shown that during arrhythmias classified as fibrillation or flutter on the basis of the surface electrogram, the activity of the single fiber may be completely irregular in some cases, with respect to frequency, amplitude, and duration of the action potential, and quite regular in others. In records obtained from atrial or ventricular muscle, however, evidence of pacemaker activity has not been recorded When records have been obtained from single fibers of the Purkinje system or the SA node, on the other hand, it can be seen that pacemaker activity often increases to such a point that many areas of membrane fire spontaneously and out of phase, this multifocal pacemaker activity distorts the single-fiber action potentials in a typical fashion (Coraboeuf and Boistel, 1953).

NEUROHUMORAL REGULATION OF HEART RATE

Interest in the regulation of heart rate has prompted many studies since the demonstration of the role of the vagus Gaskell (1886) first showed that the injury potential of the frog heart ...

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el ... studies of single atrial fibers have

provided ample confirmation of earlier results (Burgen and Terroux, 1953; Hoffman and Suckling, 1953) and added some new information. Only recently, however, have studies of single pacemaker fibers in the sinus venosus of the frog demonstrated the changes in transmembrane potential directly responsible for vagal slowing and arrest (del Castillo and Katz, 1955; Hutter and Trautwein, 1955).

During vagal stimulation, the slope of the slow diastolic depolarization of the sinus pacemaker is decreased, and with stronger vagal activity, the slope is reversed in sign so that hyperpolarization results (Fig. 2-11A). The threshold potential is not significantly altered during vagal stimulation; slowing or arrest, therefore, results from a change in the rate at which the transmembrane potential approaches the threshold level. It has been noted that the change in membrane potential resulting from a vagal stimulus of fixed strength is greatest during the phase of repolarization and slowest in onset just prior to the upstroke of the spontaneous action potential. The maximum hyperpolarization resulting from vagal stimulation has been reported as amounting to 23 to 33 mv. This amount of hyperpolarization brings the membrane potential of the pacemaker to a value that approximates the resting potential of atrial muscle. Action potentials arising from a pacemaker slowed but not stopped by vagal stimulation are decreased in amplitude and duration The latter change, however, is much less marked than shortening seen in action potentials of nonpacemaker atrial fibers during vagal activity (Hoffman and Suckling, 1953).

The action of *acetylcholine* on pacemaker fibers of the mammalian SA node is similar in many respects to the vagal effects just described for the sinus venosus of the frog Employing a preparation of rabbit atrium, West (1955) and West et al. (1956) have shown

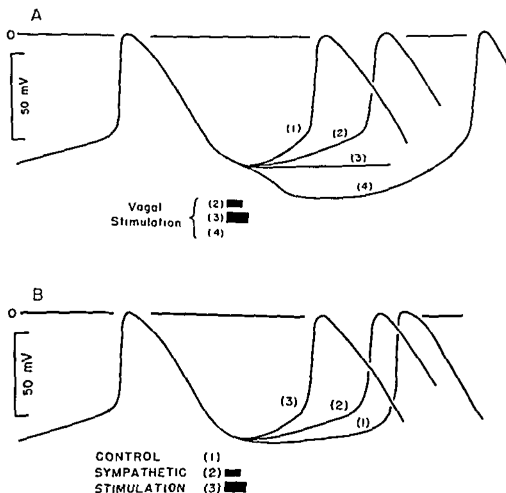


Fig. 2-11. Schematic representation of transmembrane potentials recorded from a sinoatrial pacemaker fiber during vagal, A, and sympathetic, B, stimulation Area of dark bars indicates relative strength of stimulation.

that acetylcholine added to the perfusion fluid decreases the slope of diastolic depolarization and increases the resting potential of pacemaker fibers In addition, the pacemaker action potentials are decreased in amplitude and duration It should be emphasized, however, that the magnitude of the hyperpolarization in this preparation is considerably less than that resulting from vagal action on the sinus venosus of the frog In further contrast, when acetylcholine causes arrest of the SA node of the rabbit heart, the membrane potential does not show persistent hyperpolarization but falls to a steady low level just above threshold (Hoffman, 1957). The absence of marked hyperpolarization such as is seen in the sinus venosus on vagal stimulation may be related to the locally effective concentration of acetylcholine [illegible] vagus on SA node

Shifts in the pacemaker site are a frequent occurrence following application of acetylcholine to the SA node For this reason, and because of the fairly diffuse pacemaker activity which has been described, it is difficult to obtain conclusive evidence relating to possible changes in the threshold potential It is clear that there is no large increase or decrease (Fig 2-11), a slight alteration, however, cannot be ruled out Since the resting potential is increased only slightly or not at all by concentrations of acetylcholine which cause slowing and arrest, it may be concluded that the primary mechanism responsible for slowing is the decrease in slope of diastolic depolarization.

The mechanism by which acetylcholine alters the slope of slow diastolic depolarization is of considerable interest. Numerous studies have demonstrated that potassium liberation from heart muscle is increased after vagal stimulation or application of acetylcholine-like substances (Howell and Duke, 1908, Holland et al, 1952). Experiments performed on small isolated bundles of muscle from frog atrium have shown a decrease in membrane resistance following addition of acetylcholine (Trautwein et al, 1956) It thus appears likely that acetylcholine slows pacemaker activity by increasing the potassium permeability of the membrane This would tend to increase the membrane potential to the potassium equilibrium potential and either prevent slow depolarization or greatly decrease its slope Studies of the rate of turnover of radioactive ions support this conclusion (Harris and Hutter, 1956).

Unfortunately, the atrioventricular (AV) node has not been studied by means of intracellular microelectrodes the mechanism responsible for delayed conduction and partial or complete block during vagal stimulation is thus open to speculation One possibility is that an increased resting potential and an action potential of lower than normal amplitude and rising velocity combine to diminish the velocity of conduction or produce complete failure of propagation through the nodal tissue. A somewhat similar alteration in propagation has been noted during vagal stimulation of an artificially driven turtle atrium (Hutter and Trautwein, 1956). If, on the other hand, there is some discontinuity in conduction from the atrium to the AV node, the mechanism of vagal action may be more closely related to that of inhibitory transmitters at neural synapses (Fatt, 1954; Kuffler and Eyzaguirre, 1955) In the case of pacemakers in isolated Purkinje fibers, acetylcholine has no demonstrable action on either the rate of diastolic depolarization of the amplitude or configuration of the action potential. This absence of effect is comparable to the result obtained from studies of dog ventricle, where the action potential is unchanged by either vagal stimulation or acetylcholine (Hoffman and Suckling, 1953) It is tempting to assume that this insensitivity of Purkinje fiber pacemakers to acetylcholine results from an absence of vagal terminals on the fiber membrane. Unfortunately, studies of the effect of innervation on sensitivity of embryonal heart muscle to acetylcholine have not been conclusive (Fingl et al, 1952, Fange et al, 1956). Alternate possibilities, however, are not immediately apparent.

The actions of sympathetic nerve stimulation and sympathomimetic agents are in general opposite to those of acetylcholine. Studies of single fibers of the sinus venosus of the frog (del Castillo and Katz, 1955, Hutter and Trautwein, 1955) have shown that sympathetic nerve stimulation increases the slope of diastolic depolarization without producing a marked change in the level of the threshold [illegible]

[illegible] an increase in both rising

provided ample confirmation of earlier results (Burgen and Terroux, 1953; Hoffman and Suckling, 1953) and added some new information. Only recently, however, have studies of single pacemaker fibers in the sinus venosus of the frog demonstrated the changes in transmembrane potential directly responsible for vagal slowing and arrest (del Castillo and Katz, 1955; Hutter and Trautwein, 1955).

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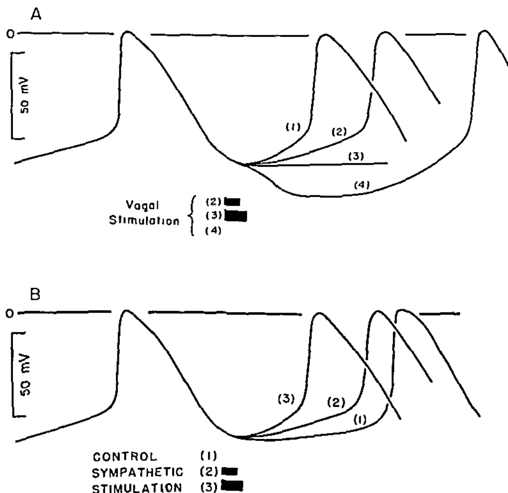


Fig 2-11. Schematic representation of transmembrane potentials recorded from a sinoatrial pacemaker fiber during vagal, A, and sympathetic, B, stimulation Area of dark bars indicates relative strength of stimulation.

that acetylcholine added to the perfusion fluid decreases the slope of diastolic depolarization and increases the resting potential of pacemaker fibers. In addition, the pacemaker action potentials are decreased in amplitude and duration It should be emphasized, however, that the magnitude of the hyperpolarization in this preparation is considerably less than that resulting from vagal action on the sinus venosus of the frog In further contrast, when acetylcholine causes arrest of the SA node of the rabbit heart, the membrane potential does not show persistent hyperpolarization but falls to a steady low level just above threshold (Hoffman, 1957) The absence of marked hyperpolarization such as is seen in the sinus venosus on vagal stimulation may be related to the locally effective concentration of acetylcholine attained, studies of the action of the vagus on the normally innervated mammalian SA node would be of interest in this regard.

Shifts in the pacemaker site are a frequent occurrence following application of acetylcholine to the SA node For this reason, and because of the fairly diffuse pacemaker activity which has been described, it is difficult to obtain conclusive evidence relating to possible changes in the threshold potential It is clear that there is no large increase or decrease (Fig 2-11), a slight alteration, however, cannot be ruled out Since the resting potential is increased only slightly or not at all by concentrations of acetylcholine which cause slowing and arrest, it may be concluded that the primary mechanism responsible for slowing is the decrease in slope of diastolic depolarization.

The mechanism by which acetylcholine alters the slope of slow diastolic depolarization is of considerable interest. Numerous studies have demonstrated that potassium liberation from heart muscle is increased after vagal stimulation or application of acetylcholine-like substances (Howell and Duke, 1908, Holland et al, 1952) Experiments performed on small isolated bundles of muscle from frog atrium have shown a decrease in membrane resistance following addition of acetylcholine (Trautwein et al, 1956). It thus appears likely that *acetylcholine slows pacemaker activity by increasing the potassium permeability of the membrane* This would tend to increase the membrane potential to the potassium equilibrium potential and either prevent slow depolarization or greatly decrease its slope. Studies of the rate of turnover of radioactive ions support this conclusion (Harris and Hutter, 1956).

Unfortunately, the atrioventricular (AV) node has not been studied by means of intracellular microelectrodes: the mechanism responsible for delayed conduction and partial or complete block during vagal stimulation is thus open to speculation. One possibility is that an increased resting potential and an action potential of lower than normal amplitude and rising velocity combine to diminish the velocity of conduction or produce complete failure of propagation through the nodal tissue. A somewhat similar alteration in propagation has been noted during vagal stimulation of an artificially driven turtle atrium (Hutter and Trautwein, 1956). If, on the other hand, there is some discontinuity in conduction from the atrium to the AV node, the mechanism of vagal action may be more closely related to that of inhibitory transmitters at neural synapses (Fatt, 1954; Kuffler and Eyzaguirre, 1955) In the case of pacemakers in isolated Purkinje fibers, acetylcholine has no demonstrable action on either the rate of diastolic depolarization of the amplitude or configuration of the action potential. This absence of effect is comparable to the result obtained from studies of dog ventricle, where the action potential is unchanged by either vagal stimulation or acetylcholine (Hoffman and Suckling, 1953). It is tempting to assume that this insensitivity of Purkinje fiber pacemakers to acetylcholine results from an absence of vagal terminals on the fiber membrane Unfortunately, studies of the effect of innervation on sensitivity of embryonal heart muscle to acetylcholine have not been conclusive (Fingl et al., 1952, Fange et al, 1956). Alternate possibilities, however, are not immediately apparent.

The actions of *sympathetic nerve stimulation* and *sympathomimetic agents* are in general opposite to those of acetylcholine Studies of single fibers of the sinus venosus of the frog (del Castillo and Katz, 1955, Hutter and Trautwein, 1955) have shown that sympathetic nerve stimulation increases the slope of diastolic depolarization without producing a marked change in the level of the threshold potential (Fig 2-11B) In addition, during the period of nerve stimulation, the action potential has been shown to undergo an increase in both rising

velocity and amplitude. Epinephrine applied to the isolated rabbit atrium similarly increases the slope of diastolic depolarization of SA pacemaker fibers (West, 1956). A frequent occurrence is the appearance of multifocal pacemaker activity with several or more fibers firing out of phase. Both epinephrine and norepinephrine have a similar effect on Purkinje fiber pacemakers: in low concentration they increase the slope of diastolic depolarization, and in higher concentrations they induce pacemaker activity in previously quiescent areas of membrane. Changes in the threshold potential are again uncertain because of frequent shifts *in the pacemaker site. An increase in the critical* level is not seen, some records, however, reveal an apparent slight decrease. The effect of epinephrine and norepinephrine on diastolic depolarization is increased by hypoxia, increased temperature, and low extracellular calcium concentrations. The mechanism of action of the sympathomimetic amines is uncertain.

OTHER FACTORS INFLUENCING HEART RATE

The effect of temperature on the electrical activity of pacemakers has been studied most extensively employing isolated preparations of Purkinje fibers (Coraboeuf and Weidmann, 1954, Trautwein et al., 1953). The most important change noted is in the slope of diastolic depolarization. When temperature is decreased from 39 to 26°C, the level of the threshold potential remains constant and the slope of slow depolarization is decreased ($Q_{10} = 6.0$). Warming from 39 to 41°C increases the slope of diastolic depolarization, at higher temperatures the preparation deteriorates. During rapid cooling, spontaneous activity is usually lost between 25 and 15°C. In most instances arrest is associated with a steady membrane potential somewhat above the threshold level, but at times repolarization fails to occur and activity ceases with the membrane potential near zero (Coraboeuf and Weidmann, 1954). Temperature effects on the pacemaker activity of the SA node of the rabbit (Marshall, 1957) have revealed several points of interest. During cooling from a control temperature of 30°C to 20 to 15°C, the resting potential falls from 65 to 50 mv, and at this level, *automaticity is lost.* Conduction throughout the atrium fails at higher temperatures and higher levels of membrane potential and is restored by the addition of acetylcholine. In the cooled node, however, acetylcholine does not cause arrest of the pacemaker.

Changes in pacemaker activity resulting from alterations in the ionic environment of the fiber are numerous and at times inconsistent. In the case of pacemaker areas of isolated Purkinje fibers, which have been employed most extensively, it has been shown that replacement of part of the extracellular sodium by substituting isosmotic quantities of sucrose for sodium chloride decreases the slope of slow diastolic depolarization. Moreover, a linear relationship *is obtained between the relative rate of fall of* potential during diastole and the fraction of sodium chloride present in the perfusion fluid (Draper and Weidmann, 1951). In the SA node of the rabbit, on the other hand, replacing up to 70 per cent of the sodium chloride by sucrose does not bring about consistent slowing, and, in many instances, the slope of diastolic depolarization is increased (Hoffman, 1957). At still lower levels of sodium chloride, the action potentials of the SA pacemaker decrease in amplitude and multifocal activity appears. In the same tissue, replacement of up to 50 per cent of the chloride by acetate or nitrate has little effect on the slope of diastolic depolarization.

When the extracellular potassium concentration is changed again, there is a difference between the behavior of the SA node and the Purkinje fiber. In the latter, a decrease in potassium concentration greatly increases the slope of diastolic depolarization and lowers the threshold potential (Fig. 2-11). Increased potassium has the opposite effect, abolishing slow diastolic depolarization and lowering the resting potential and action potential amplitude (Brooks et al., 1955). The SA pacemaker of the rabbit heart is in sharp contrast. Low and high potassium levels have little effect on either the slope of diastolic depolarization or the level of the threshold potential (Hoffman, 1957). In addition, the resting potential of the SA pacemaker is not altered to the same extent as that of adjacent atrial fibers when potassium is varied from one-quarter to five times normal. Under both extremes, pacemaker activity persists *although propagation throughout the* atrium has been lost. These findings suggest that the insensitivity of SA fiber to changes in

extracellular potassium concentration may result from low membrane permeability to this ion, as mentioned previously.

The response of the fiber to changes in potassium are strongly influenced by the *calcium* concentration present (Hoffman and Suckling, 1956) The enhanced rhythmicity resulting from low potassium is thus diminished if the calcium concentration is simultaneously lowered Similarly, the changes in resting potential which result from elevated or lowered potassium can be partly antagonized by the appropriate change in calcium level When the calcium concentration alone is varied, the effects on Purkinje fiber pacemakers are clear Between concentrations of 0 5 to 10 0 mM/liter, the only important modification is in the level of the threshold potential, the slope of slow diastolic depolarization remaining constant (Weidmann, 1955b) Slowing in calcium-high solution results from a lowered threshold potential, and acceleration in calcium-poor solution from a higher threshold level (Fig 2-8) If the calcium concentration is decreased below 0 5 mM/liter, the slope of slow depolarization is increased and previously quiescent areas develop pacemaker activity These changes, however, are not reversed on returning to normal solution In the case of the SA pacemaker, the direction of the changes resulting from alterations in calcium concentration are the same as those just described, but again the sensitivity of this tissue appears to be less marked than that of Purkinje fibers The effects of *magnesium* on pacemaker activity are slight A marked excess has an action similar to that of calcium, but complete depletion of this ion is without apparent action on either the level of the threshold potential or the slope of slow diastolic depolarization

The effects of *hypoxia* have been studied employing pacemakers in isolated Purkinje fibers and preparations of the rabbit SA node In both cases low oxygen tension augments the slope of diastol[illegible]

[illegible], are variable. With severe hypoxia, quiescent areas develop slow diastolic depolarization, and multifocal pacemaker activity appears These effects of hypoxia are reversed on returning to normal conditions only if the test period is not excessively prolonged The action of an elevated carbon dioxide tension is similar to that of hypoxia: the rate of diastolic depolarization is increased, and multifocal pacemaker activity appears (Coraboeuf and Boistel, 1953) Alterations in pH resulting from changes in the concentration of bicarbonate markedly alter the pacemaker activity of Purkinje fibers The direction of the change is such that with low bicarbonate, the slope of diastolic depolarization is increased When Purkinje fibers are overstretched, pacemaker activity is enhanced, the change in this case is most prominent in the slope of slow diastolic depolarization

The effects of a number of *pharmacologic agents* on pacemaker activity of single fibers have been studied employing intracellular microelectrodes Local anesthetics, quinidine, procaine amide, and other antifibrillatory agents, all have a similar action in that the slope of slow diastolic depolarization is decreased (Cranefield and Hoffman, 1958) In toxic concentrations, on the other hand, the antifibrillatory agents increase the rate of fall of potential during diastole and initiate multifocal firing The effects of quinidine and procaine amide are the same on spontaneous pacemakers and on pacemaker activity induced by epinephrine, norepinephrine, or hypoxia. The effects of *digitalis* have been studied employing the SA pacemaker of the rabbit. In this preparation, concentrations of digitalis which abolish propagated activity throughout the atrium permit the continuation of normal rhythmic activity in the pacemaker fibers It is to be hoped that many more studies of the action of drugs on pacemaker activity or heart rate will be performed employing techniques which permit direct visualization of the electrical activity of the pacemaker fibers themselves.

CONDUCTION

Basic Concepts. The question of propagation in cardiac muscle has been reexamined in view of information concerning the passive electrical properties of the cardiac fiber membrane and the transmembrane potentials of single fibers (Weidmann, 1956). Although certain quantitative data are not available, it is nevertheless possible to form a qualitative evaluation of propagation in the cardiac syncytium in terms of the core conductor and local circuit theories (Hermann, 1905, Katz, 1947) Because of the insulating properties of the membrane, a local-

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Hoffman, 1957) and that, in some areas, there may be local block and failure of propagation. The slow conduction is undoubtedly related to the low resting potential and low rising velocity of the pacemaker fibers (see above). Records from single fibers show a gradual transition in the form of the action potential within the node, and a more abrupt transition to normal atrial action potentials at the periphery. The spread of excitation within the node has not been mapped in detail by means of microelectrodes, but the available records (West, 1955) indicate that propagation proceeds in a reasonably uniform manner from the initial pacemaker site.

Surface recording techniques have been employed to restudy the electrical activity of the SA node and atrium of the dog heart (van der Kooi *et al.*, 1956). Bipolar records from the SA node show first low, slow biphasic waves and then larger, faster polyphasic waves preceding the activation of the atrium. The first complex is most likely an indication of distant electrical activity in the node, showing the usual spatial decrement, and the second complex the result of somewhat asymmetric spread in the vicinity of the recording electrodes. The direction of the activation wave front cannot be determined from records of this type. The spread of activity from the node throughout the atrium proceeds in a reasonably uniform manner with simultaneous involvement of the full thickness of the atrial wall. There is some indication that propagation along thick muscle bundles is faster than in the thinner parts of the wall (van der Kooi et al., 1956). Possible contributions from specialized conducting fibers have not yet been demonstrated conclusively.

2. *Atrioventricular node and conducting system.* Records of the transmembrane potentials of single fibers of the AV node have not been obtained, and the mechanism of nodal delay is still uncertain. Surface records of electrical activity in this area have been obtained by means of contiguous punctate bipolar electrodes mounted on fine needles (van der Kooi et al., 1956, Scher et al., 1955). Such records demonstrate activity quite similar to that shown by the SA node, consisting of low-voltage, polyphasic deflections beginning late during atrial depolarization and preceding the onset of ventricular activity by more than 50 msec. Most likely this polyphasic complex is similar in nature to that described above for the SA node.

The transmembrane potentials of single fibers in the *Purkinje system* have been recorded from hearts of a number of species (Cranefield and Hoffman, 1958). Such records show only a slight difference in the action potential duration of fibers from the false tendons of right and left ventricle and a more marked transition into records typical of ventricular muscle when fibers are located in the papillary muscles or the ventricular endocardium. The finding that typical Purkinje fiber action potentials are obtained from the false tendons of the heart of the dog and cat, as well as of ungulates, is at variance with some histologic studies (Glomset and Glomset, 1940). Isolated preparations of Purkinje fibers have been employed for a large number of electrophysiologic and pharmacologic studies. These fibers contrast with ventricular muscle not only in that they have a higher conduction velocity and an action potential of longer duration, but also in their tendency to develop intrinsic rhythmicity and their sensitivity to hypoxia, changes in extracellular ions, stretch, and other factors (Cranefield and Hoffman, 1958). Studies of reentrant arrythmias have led one group of investigators to postulate the existence of a dual AV transmission system consisting of slowly and rapidly conducting elements (Moe *et al.*, 1956). While all workers agree that activity is carried from the AV node to the ventricles by the Purkinje system, there is disagreement as to whether activation of muscle fibers by Purkinje fibers occurs only at the endocardium (Scher et al., 1955) or within the inner third of the ventricular wall (Durrer et al., 1955).

Activation of the Ventricular Muscle Mass. Plunge electrodes and other techniques have been employed extensively to study the sequence of activation of the septum and free walls of the ventricles. At present, there is considerable disagreement between the interpretations of various workers, and the original articles should be consulted.

ized change in transmembrane potential, due to either an applied stimulus or the depolarization of a normal pacemaker, results in a longitudinal potential difference. This in turn generates a longitudinal current flow in the myoplasm and extracellular fluid, the local circuit current, which lowers the transmembrane potential of areas adjacent to the initial depolarized locus. If this induced change in potential reaches the threshold level, a self-sustaining, all-or-none depolarization—the upstroke of the action potential—supervenes. This new depolarization acts as the current source for additional longitudinal currents which spread farther along the fiber, again lower the transmembrane potential to the threshold level, and thus continue the phenomenon of propagation. It has been shown that there is a considerable safety factor in the propagation of an impulse in cardiac muscle (Hoffman et al., 1957), as has been previously demonstrated for nerve (Hodgkin, 1937). In the cardiac fiber, the normal propagating action potential is four to eight times the threshold requirement and is capable of stimulating adjacent tissue not only when it is in the fully recovered state but as soon as the effective refractory period of that tissue ends

It has been known for many years that the velocity of conduction varies in different areas and different fibers of the heart In terms of the local circuit theory of propagation, four major factors influencing conduction velocity should be emphasized

1 *Fiber diameter.* Changes in the diameter of a fiber alter the cross-sectional area and thus influence the longitudinal resistance to current flow. With a greater cross-sectional area, the resistance is lower, local circuits tend to spread farther from the current source, and conduction velocity is increased A clear example of this effect is seen when a comparison is made between velocity of propagation in fibers from dog ventricle (1 m/sec 15 μ diameter) and dog Purkinje system (2 to 3 m/sec 30 to 40 μ diameter), or between Purkinje fibers of dog and ox heart, in the latter, the conduction velocity and diameter are 4 m/sec and 70 μ (Cranefield and Hoffman, 1958).

2 *Threshold potential* Changes in the level of the threshold potential have a marked effect on the velocity of conduction If the threshold potential falls from −70 to −60 mv, the local circuit currents will have to lower the transmembrane potential of adjacent areas by an additional 10 mv, and thus the velocity of propagation will be slowed. Alterations in the extracellular concentration of calcium have been shown to act in this manner

3. *Membrane capacity* Changes in membrane capacity, such as might result from stretching heart muscle, will strongly affect conduction velocity. In most cases, however, the change in capacity is accompanied by alterations in other parameters For example, with overstretch, the increase in velocity resulting from lower membrane capacity is probably more than offset by the concomitant decrease both in fiber diameter and in amplitude of the *resting potential (see below).*

4 *Inward current density.* Any factor which diminishes the density of inward Na+ current across the depolarized membrane will effectively decrease conduction velocity. While this effect could be brought about by a lower Na+ concentration in the extracellular fluid, the change most frequently considered is a decrease in the amplitude of the action potential It should be emphasized that a slower velocity of depolarization during the upstroke of the action potential will have an action similar to that of a lower amplitude. Also, a lower resting potential, because it lowers the force which drives Na+ across the active membrane, will similarly diminish the velocity of propagation. It should be remembered, moreover, that a low resting potential usually decreases the rising velocity and amplitude of the action potential through the effect of potential on available sodium carrier (Weidmann, 1955a).

Spread of Excitation. The spread of excitation throughout the heart has been reinvestigated by means of new techniques, several of which have supplied additional information In addition to the use of intracellular microelectrode, mentioned above, one must consider the multiple-contact needle electrode, employed in somewhat different forms by a number of investigators (Sodi Pallares et al, 1951, Prinzmetal et al, 1953, Durrer et al, 1953, Scher et al, 1953) Although none of the older concepts concerning the sequence of activation of different areas of the myocardium has been completely superseded (Lewis and Rothschild, 1912, Harris, 1941), use of these techniques has provided some additional information of interest.

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no attempt will be made to describe the experimental basis upon which it rests.

The cell membrane possesses *selective permeability*, being freely permeable to K^+ and Cl^- and, at best, only sparingly permeable to Na^+. The ionic gradients may be more apparent than real, cellular metabolism may, in the form of a "sodium pump," account for the disparity of Na^+ concentration within and without the cell Briefly then the system is maintained at the potassium potential by a *dynamic* type of Donnan system. Both K^+ and Cl^- assume their intra- and extracellular concentrations under the Donnan equilibrium effect. The marked difference between the amount of chloride and potassium within the cell is due to the high intracellular concentration of anions The inequality could be roughly set forth in the following manner

$$\frac{(Ki)}{(Ko)} = \frac{(Clo)}{(Cli)} = 20\text{-}50$$

where (Ki) and (Ko) are concentrations of potassium within and without the cell, similarly, the chloride ion concentrations are given by (Clo) and (Cli).

Whenever a Donnan equilibrium exists, a *potential* is generated across the *membrane* The following formula shows that *this potential* depends on the concentration ratios of the diffusing substances:

$$Er = \frac{RT}{F}\log\frac{(Ki)}{(Ko)} = \frac{RT}{F}\log\frac{(Clo)}{(Cli)} \qquad (1)$$

For the meaning of R, T, and F see the reference of F. N. Wilson

It is not difficult to see why a potential difference must come into play *if the system is* finally stabilized If the concentration (*or*, more correctly, activity) were fifty times greater [illegible]

would bombard the membrane fifty times as frequently as the extracellular potassium. The potential established (about 100 *mv*) neatly balances this outward flux In other words, a chemical system is driving the K^+ *ions out* and an electrical system is driving them in, thus, an electrochemical gradient has been *established* The total work of transportation of K^+ *ion across* the membrane in either direction is zero Sodium during this time is being extruded *by means of* what has become known as the *sodium pump*. During rest, sodium would, by its own electrochemical *gradient*, seep into the cell; it could only be by dynamic metabolic processes that sodium is pushed out against the gradient.

If the resting potential is disturbed, as for example by a cathodal current, the membrane suddenly develops a high specific permeability to sodium The steep preexistent gradient discharges sodium into the cell, and this ionic flow further reduces the membrane potential by alteration of charges across the capacity of the membrane. The cyclic change *of charge* and potential is exceedingly rapid *in its evolution*, being limited finally by a new *electrochemical* gradient, the sodium potential *is given* by $(Nai)/(Nao) = 1/10$. The latter expression when substituted in Eq (1) will give a negative value, indicating, as experimentally determined, a current reversal The sodium potential becomes vitiated by two processes, the decrease in sodium mobility and the outflow of K^+ along its electrochemical gradient. The gain in sodium and loss of K^+ is compensated *for* by the action of the sodium pump. The pump could theoretically extrude more sodium *while pulling* K^+ *in*

Grundfest has presented a serious criticism of the theory, preferring to consider the *membrane resting potential* as arising in the action of the sodium pump rather than in a Donnan equilibrium involving K^+ ion concentration *on* either side of the membrane. This view *arose* when by profoundly altering the external and internal K^+ (by microinjection), no change in resting potential could be elicited The resting potential was altered only when the K^+ *ion* concentrations were varied to such an extreme *that* the spike height and propagation were *affected* This relationship suggests some mutual *interdependence* between the spike and the *sodium* pump Hodgkin and Keynes have *shown that* the pump can be deactivated by DNP (dinitrophenol) with no appreciable change in *the action* potential, this would eliminate the attractive *idea of the* temporary stoppage of the sodium pump to account for the *spike*

While the appeal of this hypothesis *rests* upon the elegance with which it explains much *experimental* data, it has not met with universal *acceptance*. Heilbrunn has stated the discontent of the general physiologist as follows. "The

5

The physiologic basis of the electrocardiogram[1]

DEMETRIO SODI PALLARES AND RUSSELL W. BRANCATO

The combined investigations of electrocardiologists and physiologists have at last made it possible to put forth a tentative synthetization of both disciplines Formerly, most electrocardiographic writings would begin by paying deference to the Bernstein hypothesis and would then never mention the name again The matter was better put by Macleod (1938), who said. "Whereas Bernstein created an ingenious but imaginary construction which might account for the observed phenomena, the argument here presented consists of logical deductions from facts ." It has become increasingly evident that the newer findings can no longer be disregarded but rather need to be incorporated into the present frame of reference Classical electrocardiography, which has its origin in the postulates of Einthoven, will perforce be developed to its ultimate conclusions by mathematicians and physicists Despite this, the role of the physician will remain unaltered, because he will still need to synthesize in order to benefit the patient

This chapter will set forth briefly the newer concept about the structure of the cell membrane and the nature of bioelectric potentials Where possible, an attempt will be made to show the manner in which these data may be incorporated into practical electrocardiography

CELL MEMBRANE

At present (1958), no unified concept as to the nature of the cell membrane exists, depending on the type of investigation, the membrane is described as an electrical apparatus, an elaborate metabolic system, or a porous sieve. Each concept merely emphasizes a different property. Structurally, the membrane is felt to be within 50 to 100 A in width and composed of a lipoid-protein complex. More information is at hand as to its electrical properties Critical experiments have been devised to measure its transverse and longitudinal resistances, capacitance, and impedance during rest and activity, and finally the transmembrane potential difference It was the ability to measure the potential gradient of the cell membrane during rest and excitation that ultimately led to the overthrow of the Bernstein hypothesis Bernstein in 1902 gave a lucid formulation as to the cause of membrane potential. The selective permeability of the membrane to potassium, which was well known at that time, was the postulated mechanism for the generation of the membrane potential The theory further had to postulate that excitation consisted of a temporary phase of nonselective membrane permeability When intracellular microelectrodes became available, a reversal of potential during excitation was observed, a fact which the theory failed to explain.

Hodgkin and Katz (1949) proposed a new ionic theory replacing that of Bernstein This theory has withstood rigorous experimental assault and, with minor modifications, serves today as an essentially correct explanation for the phenomena of nerve and muscle impulses. The theory will be broadly summarized while

[1] Further details about the electrocardiogram will be found in Part 4, Chap. 1. *Editor.*

of repolarization Woodbury et al have described a repolarization overshoot which they called "hyperpolarization." Where this was observed, the membrane potential was greater during early diastole (electric) than the resting potential noted in late diastole

Since the process of repolarization is by no means simple and includes a phase of overshoot, the more general term *recovery* is preferable

Electrical Field Surrounding the Heart during Activity. Until now, a physiologic fiction has been covertly imposed upon this analysis Both processes of activation and recovery were treated as occurring instantaneously. If this were true, minimal currents would be generated It has been shown that during rest no potential differences exist in the medium, likewise, during complete activity, no potential differences would be recorded It is just because both activity and recovery occur in a graded, sequential manner that measurable currents are produced For the moment, only the process of activation will be considered, with slight modifications, imposed mainly by the speed of the reactions involved, the same analysis could equally hold for the recovery process In Fig 2-12B, a single muscle fiber is immersed in a bounded, conducting medium The disk within the cell represents the activation process moving along the fiber, the resting portion being indicated by a positive sign, the activated by a negative Since a difference in potential has been established, current will flow. As the medium is a conducting one, the amount of current flowing through it is proportional to its *dielectric constant* If two arbitrary points

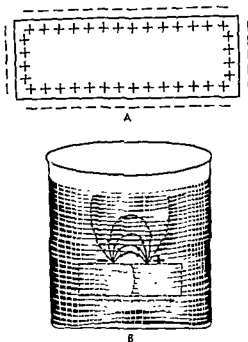


Fig 2-12. A. Activated cell reversed polarization B A single muscle fiber is immersed in a conducting medium.

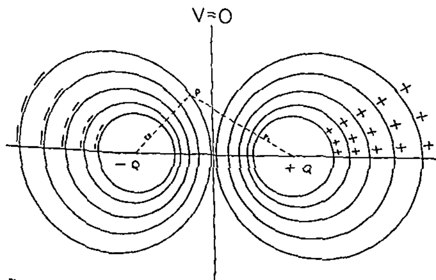


Fig 2-13. A dipole arrested in its motion.

work of these investigators has been a model of precision and ingenuity, but for the most part the conclusions that have been reached are not acceptable to a general physiologist whose background and training have conditioned him to believe that the behavior of protoplasm is fundamentally similar in all types of living systems." He then proposed a physicochemical concept of the cell membrane in which alterations in pH affect the anion- and cation-binding power of cell proteins. In essence Ca and Cl come to play the major role in the generation of bioelectric potentials. These ideas, which have been crudely sketched, arise because the theory of Hodgkin and Katz runs into serious difficulty in explaining certain critical facts.

It would thus seem that the new and accepted theory will be subjected in the future to either profound change or complete overthrow. At this stage, however, it will serve best to use the Hodgkin model, appreciating its limitations.

FUNDAMENTAL ELECTRICAL CONSIDERATIONS

The contemporary conceptions of the fundamental bioelectrical phenomena responsible for activation of the muscle cell have been briefly treated. The necessary electrical consequences as they manifest themselves according to the conditions imposed during registration will now be mentioned. Regardless of the mechanism involved, the cell, from an electrical viewpoint, is a closed surface with equal but opposite charge distribution (*positive on the outside, negative inside*) over its entire surface. The cell, or cells, is immersed in a medium which is not necessarily homogeneous. During the resting phase, an exploring electrode anywhere within the medium records the same potential, that this is so follows from consideration of the solid angle. Because of the absence of potential difference within the surrounding medium, no current can flow. Why then is no current flow produced by the membrane potential? The answer is that the membrane during rest is considered to be a nonconductor (dielectric). However, when the dielectric property is lost, as during stimulation or at a zone of injury, then a current flow would become manifest across the cell membrane. It is *precisely this current, contributed to by millions of cells, that is measured in electrocardiography.*

Chemical Events during Activation. Hodgkin and Huxley (1952b) have proved that when the membrane potential is suddenly reduced (*depolarization*), the initial pulse of current through the capacity of the membrane is followed by sodium and potassium currents moving down their own electrochemical gradients. The first current that flows consists of sodium ions; since when the cell is resting, the concentration of these ions is greater outside than inside the cell, *the flow of current is from the exterior to the interior of the cell,* thus depolarizing the membrane still further, until the membrane potential reverses its sign and approaches a value at which sodium ions are in equilibrium. Potassium current starts flowing shortly after the beginning of sodium mobilization. Since the concentration of potassium is greater inside the cell than outside, *the flow of this current is directed from within outward.* When it exceeds the sodium current, it starts the repolarization of the membrane, as described below.

Electrical Events during Activation. The ionic fluxes and the postulated mechanism have been described. A different line of approach is that taken by Curtis and Cole (1941), who, studying the membrane from its electrical point of view, made certain crucial measurements. Activation brings in its wake not only the collapse of the resistance of the membrane to zero potential (depolarization) but also a frank reversal of potential, so that *the outside of the cell becomes negative while the inside becomes positive.* This reversal phenomenon has been termed "overshoot"; it is more transient and is quickly obliterated by the forces responsible for the recovery process of the membrane. That the membrane is profoundly altered by the excitation process is seen in the works of Curtis and Cole, who showed a fiftyfold decrease in membrane resistance, or an increase in conductance 200 times the resting value.

For purposes of analysis, the cell during the reversal or overshoot phase may be electrically depicted as in Fig. 2-12A.

Electrical Events Characterizing the Recovery Phenomenon. The total sum of the forces responsible for restoring the membrane to its resting characteristics is known as the *process*

of repolarization Woodbury et al have described a repolarization overshoot which they called "hyperpolarization" Where this was observed, the membrane potential was greater during early diastole (electric) than the resting potential noted *in* late diastole

Since the process of repolarization is by no means simple and includes a phase of overshoot, the more general term *recovery* is preferable

Electrical Field Surrounding the Heart during Activity. Until now, a physiologic fiction has been covertly imposed upon this analysis Both processes of activation and recovery were treated as occurring instantaneously. If this were true, minimal currents would be generated It has been shown that during rest no potential differences exist in the medium, likewise, during complete activity, no potential differences would be recorded. It is just because both activity and recovery occur in a graded, sequential manner that measurable currents are produced For the moment, only the process of activation will be considered, with slight modifications, imposed mainly by the speed of the reactions involved, the same analysis could equally hold for the recovery process In Fig 2-12B, a single muscle fiber is immersed in a bounded, conducting medium The disk within the cell represents the activation process moving along the fiber, the resting portion being

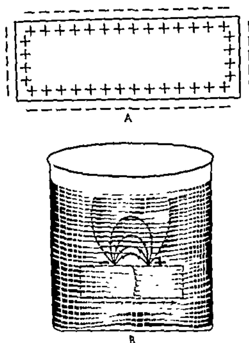


Fig. 2-12. A Activated cell, reversed polarization, B A single muscle fiber is immersed in a conducting medium

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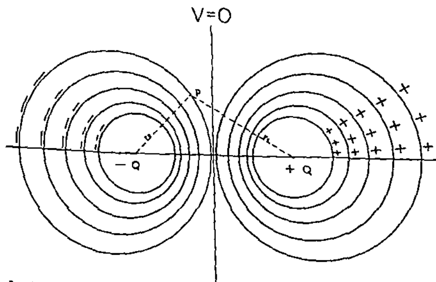


Fig 2-13 A dipole arrested in its motion.

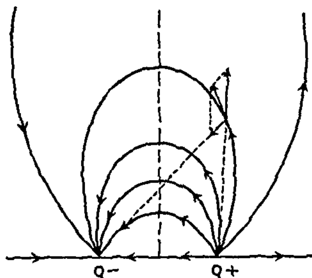


Fig. 2-14. Flow of current between anode and cathode. (Modified from Atwood)

are considered at either side of the crest of the activation wave, from one emanates the greatest flow of current from cell to medium, while the other, just behind the wave, is the recipient of the greatest flow from medium to cell By convention the former point, which is positive, is called the "source," while the latter, negative, is called the "sink" What is produced then is a *dipole*, which in conventional electrical terminology is a point of positive charge separated by a small but finite distance from a point of negative charge. A doublet is a mathematic concept calling for the distance separating both charges to be infinitely small.

It is now possible to replace the real activation process which smoothly travels along the cell, with a convenient, though fictitious, construction, the dipole, which can also be considered as traversing the fiber The dipole concept implied in the works of Einthoven arises from a different approach, which will be discussed below.

If at any instant the dipole were frozen in its motion, it would set up a number of equipotential surfaces similar to those seen in Fig 2-13. Current flows between points of different potential, and the amount of current is greater in the regions with greater difference. In Fig 2-14, this maximum flow occurs between anode and cathode, at a point just above the crest of the activation wave (see also Fig 2-12B)

Further consideration of Fig. 2-13 reveals another important point: the potential approaches zero at points distant from the tissue, regardless of the actual orientation of the dipole. This is further brought out by the formula for the potential of any point within the conducting medium

$$Vp = \frac{+Q}{r_1} + \frac{-Q}{r_2}$$

where $+Q$ and $-Q$ = the strengths of source and sink of the dipoles

r_1 and r_2 = the respective distances from $+Q$ and $-Q$ to point P

At a point P where r_1 and r_2 are very large, it is evident that Vp would approach zero. When, however, r_1 and r_2 are small, the potential is correspondingly large. If r_1 is smaller than r_2, the potential is positive, while it is negative if r_1 is greater than r_2.

On the above principles were based the early precordial electrocardiograms Two electrodes were chosen, one relatively close to the heart, the other attached to one leg (relatively distant). Subsequent terminology refers to the former as the "*exploring*" *electrode*, to the latter, as the "*indifferent*" *electrode*. The "indifferent" electrode was considered to be at zero potential, for if both r_1 and r_2 became very large, this consequently became zero. Actually this concept is only partially correct, for the actual values of r_1 and r_2 do not make the potential zero

Wilson was aware of this when he wrote: "Since we are recording only those potential variations produced by the heart beat, we may regard any point whose potential is not influenced (or is influenced to a negligible degree) by electrical forces within the heart as of zero potential" Later he elaborated a means to circumvent this objection by the introduction of the concept of the "central terminal"

It is now necessary to discuss the implications of the material presented so far. Two concepts are involved, each unique, each with its own set of consequences When the source of current is mentioned, reference is to each of the numerous activation waves and specifically to that localized area separating the active from the nonactive membrane. As a consequence of the innumerable sources, a current is distributed throughout the volume conductor of the body. The field will vary instantaneously according to the electrical energy being generated at whatever polarized interfaces exist at

that given moment The field reflects only the activity transpiring at these polarized surfaces The importance of this concept can be seen in what is meant by intrinsic and extrinsic phenomena If a recording electrode were placed directly on the heart, it would come in contact with a source only at that very instant in which the activation process passed directly beneath it The electrical manifestation of this event is called the *intrinsic deflection*. Whenever, during the entire cycle, the activation wave is approaching or receding from the site being explored, the electric phenomena recorded are called *extrinsic phenomena* The exploring electrode is recording merely the potential variations of the field induced in the *body volume conductor*, not those occurring at the site of the activation wave It should be understood that any portion of the heart, along with the cardiac chambers and great vessels, is merely a passive conductor of current except when it is the site of activity. Finally it should be remembered that in clinical electrocardiography, the potential variations occurring in the field are measured

The above conclusions were reached by Wilson and Craib Both concurred in the idea of an analysis based upon the distribution of currents in a volume conductor From this point of view, the process of activation may be considered as the crest of a wave preceded by a positive pole (source) and followed by a negative pole (sink) The process of activation would then take the form of a dipole moving along the outer aspect of the cell membrane and the process of recovery can be similarly viewed Since the phase of reverse potential is very transitory, the forces responsible for recovery quickly restore the membrane to its resting potential Wherever the membrane potential of a cell has been restored, a potential gradient will be established with points still in the activated phase For the same reasons that a dipole was a good analytic tool to comprehend the activation process, a dipole of recovery can also be postulated However, in this instance, the negative end would precede the positive as it progresses along the cell membrane In addition, the speed of recovery being slower than that of activation, the path followed by the wave of recovery can be either that following the activation process or one quite independent of it. It is well known that

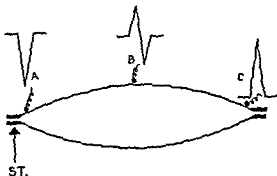


Fig. 2-15. Muscular strip immersed in a volume conductor. Stimulation at left end (see text).

one may modify or even reverse the sequence of recovery while leaving the order of activation completely unchanged

These concepts may be applied to a very simple case In Fig. 2-15 is shown a muscle strip immersed in an extensive homogeneous volume conductor Recording electrodes are placed at points *A*, *B*, and *C* within the medium; these electrodes are connected in turn to the positive pole of a galvanometer The circuit is completed by placing another electrode, connected to the negative terminal of the galvanometer, at a remote point in the medium wherein potential variations are negligible If the muscle were stimulated at its left end, the complexes recorded at *A*, *B*, and *C* would be those presented in Fig 2-15 These curves are easily explainable by the dipole concept, if one considers the dipole as originating at the point of stimulation (*A*) and moving along the fiber toward C Point A would consistently be exposed to the tail, or sink, of the dipole, giving continued negativity during the entire activation process The complex at *B* is diphasic, for as the dipole approaches this point, positive potential variations of increasing magnitude are recorded; then abruptly, as the crest of the activation process passes *B*, maximum negativity is recorded. From the time the dipole passes B, the recording electrode is located in a field of decreasing negative potential, variations accounting in turn for the return to the base line At C the electrode is always in advance of the oncoming wave front, and consequently a solely positive complex is inscribed Curves having a striking resemblance to those now discussed were recorded by Wilson on the atrium of a dog's heart An electrode placed at the superior vena cava would be similar to electrode A, since impulse formation in the SA node is close by On the other hand, a diphasic curve is recorded at a point midway between the upper end of the sulcus terminalis and the tip of the left atrial appendage

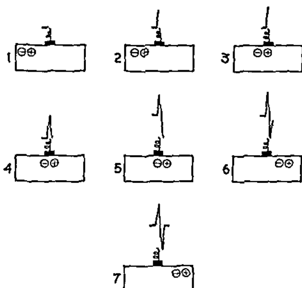


Fig. 2-16 Different patterns recorded by differently placed electrodes (see text).

In the authors' studies on intracavitary potentials, tracings have been observed that lend themselves to a similar interpretation. When the electrode was placed at the level of the superior vena cava near the SA node, *negative* P waves were recorded When the exploring electrode was advanced to the level of the inferior vena cava, the P waves were almost always *positive*, intermediate positions between these two gave diphasic P waves In a case of interatrial septal defect, the electrode was passed into the left atrium, where the characteristic P wave was one of almost unmixed positivity

These simple ideas are of great value in studying the path of the activation process in the heart Wilson and associates found that the complex representing ventricular activation (QRS) is entirely negative in the left ventricular cavity of the dog, while predominant negativity preceded by a small R wave is the pattern of the right cavity. This proves that activation must everywhere be spreading away from the left cavity, confirming Lewis and Rothschild's (1915) findings of endocardial to epicardial spread. The small R wave recorded in the right ventricular cavity is explained by an early activation of the septum with left to right spread, direct experimentation (Sodi Pallares et al.) has proved this to be correct. The major negativity in the right cavity is due to endocardial to epicardial spread of the activation process.

A more detailed analysis is presented in Fig 2-16. In this scheme, the progress of the dipole has been initiated and is advancing toward the exploring electrode; no change of potential is recorded because the dipole is incapable of exerting a significant influence at this distance. As the dipole approaches the electrode (2), the greater proximity to the positive pole source causes an initial positivity (upward deflection). Maximum positivity is recorded at (3), for at that instant the electrode is just astride the crest of the activation process (the source is nearest to the recording point). In (4) is represented the situation when the electrode is equidistant from both source and sink; zero potential, or return to the base line, is manifested At the moment when the electrode is directly above the sink (5), the greatest negativity is recorded As the wave of activation moves away from the exploring electrode, decreasing negativity is inscribed, and the tracing returns to the base line. The base line is reestablished in (7) by virtue of the great distance between the activation process and the recording point According to an electrocardiographic convention, the positive deflection is called R, the negative deflection S, and a negative deflection preceding R, Q

From the above, it can be appreciated that when a positive deflection is inscribed in the electrocardiogram, the activation process is approaching that particular lead, conversely a negative deflection implies that the process is moving away from the electrode.

Recovery Process. The analysis of the curve of recovery is similar to that made for the process of activation The different aspect could be explained by a reversed dipole, having the negativity (sink) ahead of the positivity (source) The result is that the final wave of Fig 2-17 is positive The following is only a partial list of the many ways in which the recovery process differs from the activation process

1. The times corresponding to the greatest

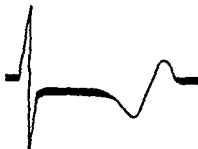


Fig. 2-17. The electrical process of activation and recovery.

differences in potential during recovery are farther apart Macleod expressed this by conceiving of the recovery dipole as being physically longer than that of the activation one.

2. The smooth, round deflection usually seen is caused by the recovery process being slower in its motion along the outer membrane

3 Generally only the positive part of the T wave is recorded Macleod's analysis of this situation revealed the earlier manifestations of the recovery process being buried in the QRS complex Bayley, on the other hand, has been able to record curves similar to those expected, that is, diphasic curves with preceding negativity

4 The regression curve is much more unstable than the activation curve External stimuli can cause profound alteration in the repolarization process while leaving activation virtually unaltered. Often the disturbance of recovery is the result of a change in direction and sequence of the wave of depolarization

The experiments of Curtis and Cole deserve discussion because they show that when one is working on isolated tissue, the electrode placement is critical These workers experimented on the axon of the squid, immersed in a shallow trough containing a small amount of a liquid conductor Impedance of the membrane was measured by the use of a Wheatstone bridge, which became unbalanced depending on changes in membrane resistance. If resistance is known, then conductance is known, thus, when resistance is at a minimum, the conductance is maximal. Conductance is maximal when the activation of the area under the electrodes has just occurred, this technique provides an excellent time marker for comparing various factors

In their first experiment, Curtis and Cole (1941), applied a small amount of potassium chloride to one end of the squid axon, and rendered the axon in that portion electrically inexcitable through chemical necrosis (a tissue may be inexcitable and still be capable of passive conduction of currents) The other electrode was placed on normal tissue, as shown in Fig. 2-18A In the second experiment, bipolar electrodes were placed together on the intact outer surface of the cell (Fig. 2-18B) In the third experiment, electrodes a and b were paired in such a manner as to constitute an indifferent electrode, with c becoming in effect the exploring electrode (Fig. 2-18C). The cells were then stimulated at the point labeled Est. The three curves registered are shown beneath each electrode placement, with a small arrow representing the point at which the impedance is suddenly reduced. Even though the curves seem different, they represent the same electrical phenomenon, i.e., the total sum of events transpiring across the membrane during activation and recovery. This totality of electrical phenomena is otherwise known as the action potential. Since these curves mirror the same event, it is proposed to seek in the following section the mathematical relationship linking them

Monophasic Action Potential. The curve in Fig. 2-18A is called *the monophasic action potential* It derives its importance from the striking resemblance it bears to the morphology of electric curves seen following an injury. Much controversy has centered about the *injury pattern*, especially in regard to the contribution of the injured tissue to the curve It is easy to show that all electric manifestations arise in the intact tissue, but it can be equally demonstrated that the presence of injury allows for these forces to be expressed in an unusual manner. The common denominator of any injury, whether thermal, mechanical, or chemical, is to render the involved tissue inexcitable and in so doing to lessen or abolish the normally prevailing transmembrane potential. It is apparent that the injury tissue cannot be a source of electromotive force while it continues to be an electrical conductor The loss of polarization is due to the fact that the injured segment no longer possesses its normal dielectrical properties, which causes the abnormal currents known as currents of injury. It is the authors' conclusion that these abnormal forces stem from the vital processes of the intact membrane, modified only by the resistance of the system.

The terminology used will be that of Curtis and Cole V_1 is the potential at the outer surface of the membrane of the intact end of the cell where the electrode is placed, V_2 is the potential at the inner surface of the membrane in the same place, V_0 is the potential of a reference electrode placed on the injured tissue,[2] r_1 is the external resistance

[2] As noted above, the authors chose the inactivated end of the cell as the origin for measurement of the monophasic action potential At this point, V_1 and V_2 have disappeared due to the

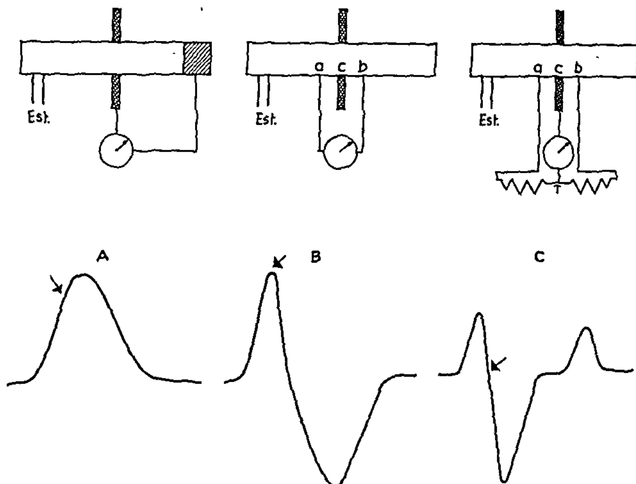


Fig. 2-18. Experiments on axon of the squid Est Point of stimulation. (Modified from Cole and Curtis.)

of the cell per unit length, r_2 is the internal resistance of the cell per *unit length*, I_1 *is the* external current flowing away from the origin at *the outer* surface of the cell, parallel to its long axis, I_2 is the internal current flowing in the same direction at the inner aspect of the cell, parallel to its long axis, I_m is the current flowing across the membrane from within outward.

In the present experiment with one electrode on normal, the other on injured tissue, the potential variations of this arrangement are given by the expression $V_1 - V_0$. Because of Ohm's law:

$$V_1 - V_0 = I_1 r_1$$

and, since $I_1 = I_2 = I_m$ by Kirchhoff's law, I_m may be substituted for I_1. Consider now the *potential differences across the intact membrane, again by Ohm's law*

$$V_1 - V_2 = I_m(r_1 + r_2)$$

effect of KCl This portion is inexcitable, but, although it cannot be a source of electromotive force, it is subject to potential variations since electric currents can flow through it.

Multiplying now by the same factor, the following is obtained:

$$V_1 - V_2\left(\frac{r_1}{r_1 + r_2}\right) = I_m(r_1 + r_2)\left(\frac{r_1}{r_1 + r_2}\right)$$

$$= I_m r_1$$

Therefore

$$V_1 - V_0 = V_1 - V_2\left(\frac{r_1}{r_1 + r_2}\right)$$

More accurately r_1 and r_2 are not constants and vary depending on the site at which they are considered, while this may change the form of the curve, the analysis is unchanged.

The design of the experiment obviously gives the potential variations existing between intact and injured tissue ($V_1 - V_0$), the foregoing analysis showed that these variations are simply the variations occurring across the intact membrane ($V_1 - V_2$) which is now susceptible to expression Thus the monophasic curve is dependent on the action potential at the normal tissue, and the contribution of the *injured* tissue is negligible

Further substantiation of this concept is given by Rosenblueth and associates Using dog and cat ventricles, both in situ and in isolated preparations, they found that the monophasic curve could be altered by heating or cooling the intact portion but was unaltered if similar thermal stimuli were applied to the injured segment By way of explanation, they introduce the idea that because of injury, an electrode placed over such tissue is in effect prolonged inside the cell, through the interval medium of the cell, and hence may be regarded as directly facing the other electrode lying on the outside of the intact portion of the cell Functionally then the electrodes are juxtaposed across the intact membrane For this reason the authors introduce the term "monotopic" as a substitute for monophasic, feeling that it indicates more adequately that the two electrodes are exploring a single region Actually the curves recorded by microelectrodes are similar to monophasic or "monotopic" curves

Certain of Wilson's experiments may seem to be opposed to the above ideas In *experiments on an extensive* volume conductor, he placed one electrode over an injured portion of the heart and another at a point sufficiently removed so as to suffer negligible potential variations throughout the cardiac cycle The recorded curve was the duplicate of the monophasic action potential Wilson concluded by stating that this curve represented the potential variations of the injured tissue itself or of the directly overlying medium

According to Rosenblueth, on the other hand, injured tissue is merely a passive conductor of currents generated in normal tissue and transmitted via the internal media to the injured region There is no basic difference of concept, because while current flow can be detected within an injured tissue, it does not necessarily have to arise there Wilson was certainly aware of this when he said, "No one supposes that the destroyed or inactivated membrane of the injured region contributes to the action potential or that voltage across this membrane changes during excitation"

Diphasic Action Potential. The experiment illustrated in Fig 2-18B has been previously discussed The curve is a result of the so-called "axial current" flowing between electrodes along the external surface of the cell, parallel to its long axis

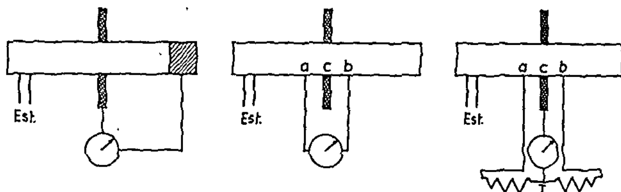
Curve of the Membrane Current. The electrical circuit of Fig 2-18C is so arranged as to give the potential T in the following manner: $V_t = (Va + Vb)/2$ This equation may be interpreted as showing that the curve recorded is a function of current entering or leaving the cell, it is quite similar to the curve inscribed using unipolar leads in a conducting medium.

Cole gave the following information: the total membrane current I_m is that of the condenser $C(\partial v/\partial t)$ added to that carried by ions i_i This membrane current is also given by the second partial derivative $\partial^2 V/\partial x^2$ of the potential along the axon.

$$I_m = C\frac{\partial v}{\partial t} + i_i = \frac{1}{r_1 + r_2}\ \frac{\partial^2 V}{\partial x^2}$$

Volume Conductors. It has been suggested so far that the curves obtained in an extensive conducting medium are different from those obtained when the electrodes are placed directly on the tissue It is necessary to clarify these differences, for clinical electrocardiography rests upon them

When a strip of muscle or nerve is suspended in air or in a shallow trough and electrodes are applied to it, the current reaching the electrodes does so via the thin film of fluid surrounding the tissue The distribution of this current ("axial current") is similar to that found in a linear conductor Thus one has a situation in which there is a negligible potential drop from points much removed from the activation crest, and no galvanometric response is recorded until the electrodes actually lie astride the activation front If this is compared with the events occurring within a volume conductor during activation, a marked difference is observed Current flows from many points of the unactivated tissue to numerous points of activated tissue. In addition, the density of current falls off the further the point is removed from the activation crest, the crest representing the point of maximal current density Since current density is directly proportional to potential difference, what actually prevails is a potential gradient along the tissue in advance of the wave front Galvanometric deflections would occur between two electrodes placed on the tissue before the activation process reached either of them Moreover this potential gradient not only applies to points on the tissue but exists throughout the whole volume conductor



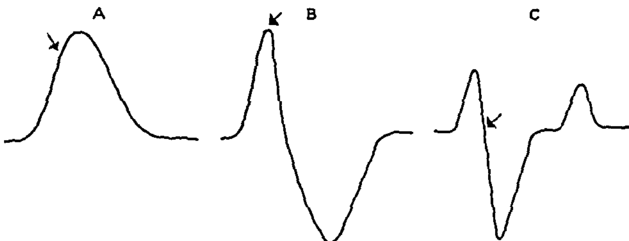


Fig. 2-18. Experiments on axon of the squid. Est. Point of stimulation. (Modified from Cole and Curtis.)

of the cell per unit length, r_2 is the internal resistance of the cell per unit length, I_1 is the *external* current flowing away from the origin at the outer surface of the cell, parallel to its long axis, I_2 is the internal current flowing in the same direction at the inner aspect of the cell, parallel to its long axis, I_m is the current flowing across the membrane from within outward

In the present experiment with one electrode on normal, the other on injured tissue, the potential variations of this arrangement are given by the expression $V_1 - V_0$. Because of Ohm's law:

$$V_1 - V_0 = I_1 r_1$$

and, since $I_1 = I_2 = I_m$ by Kirchhoff's law, I_m *may be substituted for* I_1. Consider now the potential differences across the intact membrane, again by Ohm's law.

$$V_1 - V_2 = I_m(r_1 + r_2)$$

Multiplying now by the same factor, the following is obtained·

$$V_1 - V_2\left(\frac{r_1}{r_1 + r_2}\right) = I_m(r_1 + r_2)\left(\frac{r_1}{r_1 + r_2}\right)$$

$$= I_m r_1$$

Therefore

$$V_1 - V_0 = V_1 - V_2\left(\frac{r_1}{r_1 + r_2}\right)$$

More accurately r_1 and r_2 are not constants and vary depending on the site at which they are considered, while this may change the form of the curve, the analysis is unchanged.

The design of the experiment obviously gives the potential variations existing between intact and injured tissue ($V_1 - V_0$), the foregoing analysis showed that these variations are simply the variations occurring across the intact membrane ($V_1 - V_2$) which is now susceptible to expression Thus the monophasic curve is dependent on the action potential at the normal tissue, and the contribution of the injured tissue is negligible.

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effect of KCl. This portion is inexcitable, but, although it cannot be a source of electromotive force, it is subject to potential variations since electric currents can flow through it

6

Physical units and concepts useful in cardiovascular research

ALAN C. BURTON

Many misconceptions can arise in hemodynamics because of lack of familiarity with the basic units and relations of the physical factors involved (pressure, work, etc.) The mathematic relations are, for the most part, extremely simple, and it is easy to calculate quantities like kinetic energy (K E) of flowing blood in absolute terms Only when these calculations have been made, can the proper emphasis be placed on the importance of various factors

In using the fundamental equations, all units ("practical units") should be translated into the single system of cgs (cm, Gm, sec) units, in order to avoid mistakes. Results, and equations, should always be tested by the dimensional rule, i e, by seeing that the total dimensions in terms of mass, M, length, L, and time, T, check on the two sides of any equation

DEFINITIONS, UNITS, AND DIMENSIONS

1. *Force* Force is defined by Newton's second law of motion as that which, acting on *mass* (or "inertia"), produces a proportionate *acceleration* (rate of change of velocity)

$$F = M \times a$$

Units Dynes = Gm cm/sec/sec

Dimensions $MLT^{-2} = M \times LT^{-2}$

2. ***Pressure.*** Pressure is defined as force per unit area of cross section, at right angles to the force. Units Dynes/cm² Dimensions: $ML^{-1}T^{-2}$.

3. ***Fluid.*** A fluid is defined as a substance which yields continuously to the slightest tangential stress (or "shear") within its interior. A fluid can be divided easily along any plane (if the fluid is *viscous*, enough time must be given) Blood is a *viscous fluid* Like most liquids, blood is a relatively *incompressible fluid*, this means that its volume changes very little indeed, even if its pressure is changed greatly Gases, in contrast, are highly compressible

4. ***Laws of Fluid Pressure.*** These are due to Pascal (1663) For a fluid at rest (i.e , hydrostatics), they are the following:

a The pressure in a fluid is *normal* to any plane [this follows from (3) above]

b It is equal *in all directions*, at a given point in the fluid

c In a fluid at rest under gravity, the pressure is *the same* at any two points in a horizontal plane

d The pressure *increases with the depth* below the free surface by the following law

$$P = \rho \times g \times h$$

Pressure = density × acceleration of gravity × depth below free surface

Units dynes/cm² = Gm/ml × cm/sec/sec × cm

Dimensions: $ML^{-1}T^{-2} = ML^{-3} \times LT^{-2} \times L$

In clinical electrocardiography, the volume conductor is the human body in its entirety. Because of the existence of a field, the movements of the dipoles of activation can be observed and their direction determined, even though the dipoles are not directly beneath the exploring electrodes. The general principle is as follows: when a dipole moves toward an electrode, positivity is inscribed; when it moves away, negativity is registered.

Another important point is that current density is relatively great when recording directly from the tissue, but falls off rapidly as the electrode is moved further and further away. For this reason extremely sensitive amplifiers are needed in clinical electrocardiography, because the current density has markedly decreased before reaching the electrodes which are placed on the limbs. However, because of this rapid fall in density, a distal electrode is relatively indifferent in comparison to one placed on the anterior wall of the heart.

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Physiologists teach this, but some of them do not seem really to *believe it!* *In aviation medicine, where g is increased* in a sharp turn, the same calculation predicts the occurrence of a "blackout." *Therefore, all pressures must be referred to the level of the heart* if they are to be compared with conventional standards. To make the correction, one should divide the distance above or below the heart (in millimeters) by 13.6 and subtract or add respectively to the pressure in millimeters of mercury.

8. *The Riva-Rocci Method of Estimating Arterial Blood Pressure.* A much-neglected requirement is *that the width of the cuff on the arm must be at least equal to the diameter of the arm.* For subjects with fat arms, the standard cuffs commercially available may not meet the requirement. If not, the artery may pass *through* an area in the arm where the tissue pressure is not equal to that in the cuff, and so escape occlusion. It has been shown that readings 30 to 50 mm Hg *too high may result* (Thomson and Doupe). Unless this caution is heeded, normotensive patients with very fat arms will be unjustly condemned to attend hypertensive clinics and probably will develop hypertension from the anxiety state engendered. As their overweight is reduced by treatment, their fictitious hypertension will appear to be less.

It must be realized that the indirect (Riva-Rocci) method happens to give approximately correct values by the proper auscultatory *criteria of* systolic pressure (first incidence of tapping sound) and diastolic pressure (change or muffling of the sound) *only in normal subjects at rest,* and that this is by accident, i.e., by a *number* of errors in opposite directions canceling each other. There is *good reason to believe that* the very high systolic readings in *patients* with arteriosclerotic arteries in the arm are considerably higher than their *true systolic pressure.* It takes considerably more pressure (tissue pressure vs. intraarterial pressure) to close them down. Nevertheless this fictitiously high value serves as a reliable indication of arteriosclerosis.

The criterion of diastolic pressure in the indirect determination has been much discussed. In spite of *recommendations to the contrary* by eminent authorities, *there is very little doubt that the change or muffling of the sound is much more reliable than the disappearance of the sound.* In the normal subject at rest both happen to be close to the true diastolic pressure, but in normal persons in exercise, or abnormal persons at rest (Roberts et al.) the disappearance of the sound is completely unreliable both on the basis of theory and on that of direct measurements by arterial catheterization. The disappearance of sound signifies that turbulence, or vibration of the vessel wall, caused by the constriction of the artery under the cuff, has disappeared. This has nothing to do with diastolic pressure, but depends on velocity of flow and diameter of vessels. The "muffling" depends on the fact that when the cuff pressure falls to diastolic pressure, there will no longer be any period when the artery is momentarily closed, so the noise becomes "continuous" instead of "staccato." Both the muffling and the disappearance should of course be recorded, *but if "disappearance" is regarded as the most reliable of* the two, many subjects with normal cardiac *function* will be put under suspicion of having aortic incompetence.

9. *Mean Arterial Pressure.* In considering the energetics of blood flow, the pulsatile nature of the flow can be ignored and a "mean systolic pressure" can be substituted for the actual systolic and diastolic pressures. The *proper mean to use is not the arithmetic mean of systolic and diastolic pressures, but a true "time mean,"* i.e.,

$$\bar{P} = \frac{1}{T}\int_0^T P\,dt$$

where T is the period of the cardiac cycle. For accurate work this should be evaluated by the area under a pressure-time graph of the pulse, approximately $\bar{P} = (S + 2D)/3$, where S and D are the *systolic* and diastolic pressures if the pulse contour is not too abnormal.

It is to be noted that it is possible *for both* the systolic and the diastolic pressures to be higher in the femoral *artery than* in the aorta, and yet for the true *time mean of* the pressure to be less (as it must because of energy loss). The approximate formula would be quite wrong *here, but* graphic determination of the mean would be *correct.*

10. *Lateral Pressure and End Pressure; Kinetic Energy (K.E.) of Flow.* When a cannula, tied into the end of an artery in an animal, or a catheter with an opening at its

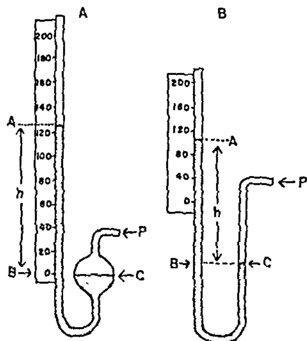


Fig. 2-19. Reference manometers for calibration. A The reservoir type. B. The U-tube type.

5. Manometers. Manometers are instruments for measuring pressure A great variety are used in cardiovascular research, including modern *electronic pressure transducers.* It is *important to realize that ultimately all* manometers must be calibrated by comparison with the basic type, which measures the height of a column of liquid (such as mercury or water) of known density (Gm/ml) [1] This is explained by (4) above, applied as in (6) Also, electronic devices are justified only because of their great "speed of response," and perhaps because of their ease of recording They have no virtue where speed of response is not involved, in which case the height of a column of fluid should be used instead

There are two types of mercury (or water) manometer, which must be distinguished

a. The *reservoir type* (Fig 2-19A) The cross-sectional area of the fluid in the reservoir *must* be many times that of the vertical tube (if a fixed scale is used), so that as the pressure changes, the level in the reservoir does not change appreciably. Pressure to be measured. P = pressure on liquid at C in reservoir (Fig. 2-19) = pressure on liquid at B in tube [same horizontal level, by law (4c)] = pressure at A (barometric) + ρgh [by law (4d)].

b. The *U-tube type* (Fig. 2-19B). The two limbs must have the same cross-sectional area (if a fixed scale is used), so that when the meniscus rises in one, it must fall in the other by the same distance. One millimeter on the scale represents a 2-mm change in h (the difference between the heights of the two columns). *This type has only half the sensitivity* of the reservoir type

One must beware of manometers of type *B* where the two limbs do not have identical cross-sectional area, or of type A where the cross-sectional area of the reservoir is not at least 100 times that of the vertical limb. If the height of the column is read from a fixed vertical scale, there will be a serious error.[2] If the scale is movable and the *difference* in height of two limbs is always measured, there will, of course, be no error.

6. Change of Millimeters of Mercury or Centimeters of Water into Dynes per Square Centimeter. This follows directly from (4d). Pressure due to a column of mercury 1 mm high = ρgh = 13 6 × 980 × 0 1 = 1,330 dynes/cm²

7. Correction of Blood Pressures to Level of the Heart. When a patient is not horizontal, the normal blood pressure in the arteries is not 120/80 mm Hg, except at the heart level. At other levels, the hydrostatic factor ρgh must be subtracted or added

Thus, the normal pressure in the arteries of the feet of a man whose feet are 100 cm below his heart, is increased when he stands by 1,000/13 6 mm Hg (74 mm Hg), taking the density of blood as 1 0 This would bring the normal arterial pressure to 194/154 mm Hg at the feet Similarly, in the arteries of the brain, say the circle of Willis, the arterial pressure is reduced by, say, 600/13 6 = *44 mm Hg (for 60 cm above the heart),* to a normal value of 76/36 mm Hg.

[1] During the war, the author had to test the claims of a charlatan, probably an enemy spy, as to a unique pressure suit for high altitude, that he had "invented" When our tests showed it to be worthless, he *countered* that the tests were invalid, because we had not used "pressure gages" but a mercury manometer!

[2] A most useful manometer for clinical use in taking the blood pressure of apprehensive hypertensive patients would be one in which the cross-sectional area of the reservoir was only, say, four times that of the vertical tube It would read 20 per cent low, yet look absolutely reliable

When, as in cardiac ejection, the pressure alters, one must use integration:

$$\text{Work done} = \int_{V_1}^{V_2} P \cdot dV$$

$$\text{Units (ergs)} = (\text{dynes/cm}^2) \times (\text{ml})$$

13. *Pressure Work of the Heart.* If this is calculated for the ventricle, by the above equation

$$\text{Pressure work per cardiac cycle} = \int_{V_D}^{V_S} P_v \, dV_v$$

where P_v = the ventricular pressure
V_v = the ventricular volume
V_S and V_D = the systolic and diastolic volumes of the ventricle

then (dV_v) must be equal to the element (dO) of the output from the heart at that particular time. The calculation must be made for the right ventricle as well as for the left ventricle, but the work of the right heart is only about one-fifth of that of the left heart, because the pressures are correspondingly lower. An integral is the area under a curve of the two variables. Thus $\int P \, dV$ is the area under the curve of pressure vs. volume of the ventricle (Fig. 2-20). The total work of the heart is the area enclosed by the loop of Rushmer's diagram (Rushmer, 1955) for the cardiac cycle, and this is the best way to estimate the ventricular work, if measurements of ventricular volume and pressure permit it. The pressure work in the aorta is less than that of the ventricle because K.E. in the aorta has been *created*, resulting in aortic pressures being lower *than* simultaneous ventricular pressures, even though the aortic valve is open.

14. *Kinetic Energy Created by the Heart.* If an element of cardiac output, dO ml, is ejected with velocity v, K.E. equal to $\frac{1}{2}\rho v^2 \, dO$ has been created.

Therefore

$$\text{Total K.E. created per cycle} = \int_0^O \tfrac{1}{2}\rho v^2 \, dO$$

In the aorta, therefore, this must be added to the pressure work of the aorta, i.e.,

$$\int_0^O P_a \, dO$$

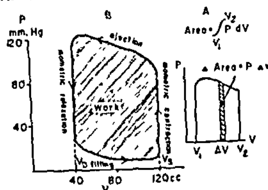


Fig. 2-20. A. How the area under a curve represents the integral. B. The pressure-volume curve of the cardiac ventricle, the area of which gives the mechanical work of the ventricle. (After Rushmer.)

where P_a is the aortic pressure. Thus, the total work of the heart (from measurements of pressures in the aorta) is

$$\int_0^O (P_a + \tfrac{1}{2}\rho v^2) \, dO$$

instead of the simpler integral for the ventricular work. For resting cardiac output, the K.E. factor $\frac{1}{2}\rho v^2$ is not more than 5 per cent of the pressure factor, but with increased cardiac output in exercise it can become important.

15. *Approximations for the Work of the Heart.* Since the true integrations are so difficult to make, many workers use a mean pressure $\bar{P}$, and a mean velocity $\bar{v}$, and state,

$$\text{Work} = \bar{P} \times O + \rho \bar{v}^2 \, O = O(\bar{P} + \rho \bar{v}^2)$$

It must be noted that, here, the mean value $\bar{P}$ should *not* be the "time-mean" pressure in the aorta, but the mean with respect to the output. Similarly, the mean velocity should not be the time-mean velocity (or the total output divided by the cross-sectional area of the aorta) but a complicated "root-mean square velocity with respect to the output," which brings us back to the original integrals. This is why the ($\frac{1}{2}$) does not appear in the above formula in the K.E. term. It is thought that this kind of mean velocity is such that $\bar{v}^2$ is twice V_m^2, where V_m is the usual time-mean velocity. This is true only for a particular type of ejection curve. Such formulas are of little validity but of some rough practical usefulness.

16. *The Load, or Energy Requirements, of the Heart.* The mechanical work of the heart is actually a very small part of the total load

end, is connected to a manometer, it records "end pressure." The K.E. of the blood flowing up against the cannula or catheter is destroyed and converted into pressure energy. The pressure recorded (end pressure) is therefore higher than that where the pressure is recorded from an opening in the side of the catheter, or when the flow is uninterrupted and pressure is recorded from the side limb of a T cannula. The difference between end pressure and lateral pressure measures the K.E. of the flowing blood. The K.E. per milliliter of flowing blood = $\frac{1}{2}\rho v^2$, where ρ is the density and v is the velocity at any instant. *Bernouilli's principle,* which is just a special case of the conservation of energy, states that the sum of the pressure and the K.E. per milliliter at a given point in a fluid is constant, i e., $P + \frac{1}{2}\rho v^2$. If the K E. ($\frac{1}{2}\rho v^2$) is destroyed, the pressure will increase by the same amount.

Take the velocity in the aorta at systole, which may be as high as 100 cm/sec in exercise:

$$\begin{aligned} \tfrac{1}{2}\rho v^2 &= \tfrac{1}{2} \times 1 \times (100)^2 \\ &= 5{,}000 \text{ dynes/cm}^2 \\ &= 3.75 \text{ mm Hg} \end{aligned}$$

The K E. at that instant would be equivalent to 3 75 mm Hg However, if the velocity is, say, 50 cm/sec, the K E equivalent is ¼ of 3.75, i e, 0.9 mm Hg Taking the mean velocity in the aorta, it is found that for resting cardiac output, the K E. is equivalent to only about 3 to 5 mm Hg In even the large arteries it soon becomes very small, and it is absolutely negligible in the arterioles and capillaries (for a velocity of 1 mm/sec, the K E. is equivalent to only 0.00001 mm Hg) [3]

The K.E. factor in the aorta is, therefore, never very important at rest, but can become appreciable in heavy exercise, since the velocity may increase fivefold with the increased cardiac output, and the K E. could then increase 25-fold (to 93 mm Hg). During the ejection phase of the cycle, the difference between ventricular and aortic pressure is a measure of this K.E., since in the ventricle there is pressure energy but very little K E.

11. Lateral and End Pressures in Stenosis, Instability, and Generation of "Flutter." The K.E. term becomes very important indeed in disease where there is stenosis of an artery, such as a coronary vessel. A local narrowing will not (until it approaches closure) decrease the total resistance to flow very much, but the velocity through the stenosis will be greatly increased. Suppose the normal velocity in a coronary artery is 30 cm/sec. The factor

$$\tfrac{1}{2}\rho v^2 = \frac{(30)^2}{2 \times 1{,}330} = 0.33 \text{ mm Hg}$$

If the lumen is narrowed at one point so that the radius is one-fourth of this, the cross-sectional area is one-sixteenth, and the velocity at that point is sixteen times as great The K.E factor is then 16^2, or 256, times as great and will amount to about 84 mm Hg. The lateral pressure will then be reduced to very little more than atmospheric. For a greater reduction in diameter, there would be nothing to keep the lumen open, and complete closure would be likely. Of course, if the stenosis closes, the flow stops, the K.E factor disappears, the lateral pressure rises, and the lumen will reopen. The cycle is repeateded indefinitely, this is the origin of "flutter," the basis of all reed instruments. Whether "flutter" occurs or not, Bernouilli's principle makes blood vessels tend to be unstable, so that a stenosis tends to persist or become worse.

12. Mechanical Work in Fluid Flow.

Work = force × distance moved by point of application of force

Units: ergs = dynes × cm

Dimensions: $ML^2T^{-2} = MLT^{-2} \times L$

$$\begin{aligned} \text{Work done by fluid pressure} &= (\text{pressure} \times \text{cross-sectional area}) \times (\text{distance moved by fluid}) \\ &= (\text{pressure}) \times (\text{cross-sectional area} \times \text{distance moved}) \\ &= (\text{pressure}) \times (\text{volume moved}) = P \times \Delta V \end{aligned}$$

[3] One popular textbook of physiology seriously discusses the application of Bernouilli's principle to the capillary, i e, that if the capillary dilated, the velocity would decrease, and the side pressure increase True, but by 0 00001 mm Hg!

Units. If ΔP is in mm Hg, and flow F in ml/sec, the resistance is in *peripheral resistance units* (PRU)

Dimensions. $(ML^{-1}T^{-2})/(L^{3}T^{-1})$.

Examples. If the two points chosen are the aorta and the vena cava, the resistance is the *total peripheral resistance* (TPR), e.g., if cardiac output = 5 liters/min,

$$F = \frac{5{,}000}{60} = 83 \text{ ml/sec}$$

$$P = \text{aortic pressure} - \text{vena caval pressure} = 100 - 5 = 95 \text{ mm Hg}$$

$$\text{TPR} = \frac{95}{83} = 1.1 \text{ PRU}$$

(This is why the resistance is expressed in these units.)

There are three forms of the relation between *R*, *F*, and *P*

(1) $R = \frac{\Delta P}{F}$ (2) $F = \frac{\Delta P}{R}$ (3) $\Delta P = FR$

The three relations are given in the device $\Delta P/FR$. When the desired parameter is covered with the finger, what is left gives the desired relation

20. *Poiseuille's Law.* The following is Poiseuille's law (1841) for steady flow of an incompressible viscous fluid in a cylindric tube of radius *r*

$$F = P \times \frac{\pi}{(8)} \times \frac{1}{\eta} \times \frac{(r^4)}{L}$$

Flow = pressure drop × numerical factor × viscosity factor × geometric factor

$$\text{Units ml/sec} = \text{dynes/cm}^2 \times \frac{1}{\text{poise}} \times \text{cm}^3$$

Everything in the law is common sense, the π because the cross section *is circular, the 8 arose* in the integrations, the flow *obviously varies* inversely as the viscosity, and as the length of the tube. The only *unexpected feature is that flow varies as* r^4, *not as the cross-sectional area*, i.e., not as r^2. Halving the diameter of the lumen of an arteriole decreases the flow sixteen times

LIMITATIONS OF THE LAW

a. the viscosity must be normal, as of a "Newtonian fluid"

b. the fluid must be *incompressible* (*different formula for a gas*)

c. the flow must be *streamlined*, not *turbulent*

Condition *b* is always satisfied, *c* is usually satisfied, but blood has anomalous viscosity, so that condition *a* is not satisfied. The viscosity factor $1/\eta$ is therefore not a constant, but depends on the other factors, as the pressure gradient *P*, or the velocity of flow. However, it turns out that this is not a serious factor, in the range of physiologic blood flows. Actual pressure-flow curves of vascular beds are *indeed far* from linear. This is *not* because of anomalous viscosity, except to a very slight extent, but because the geometric factor (r^4/L) is also not constant. Since the vessels are extremely distensible, the radius *r* increases when the pressure rises. *It is still true that for any set of* conditions of pressure, the flow is given by the Poiseuille formula, but it must be interpreted as the "effective viscosity" under those conditions, and the geometric factor (r^4/L) as that pertaining to that particular set of *pressures*

21. *Resistance, According to Poiseuille's Law.* By Poiseuille's law,

$$R = \frac{P}{F} = \frac{8}{\pi} \times \eta \times \left(\frac{L}{r^4}\right)$$

The resistance of any vascular bed, therefore, depends on the product of the effective viscosity (appropriate to the rate of flow) and the geometric factor appropriate to that set of pressures in the vessels. If then, after a physiologic or pharmacologic procedure, the resistance increases, it usually means that the geometric *factor* (L/r^4) has increased (since in most experiments the viscosity changes little). This *means that there has been a narrowing of the* vessels (i.e. "vasoconstriction"). Thus far the deduction is unequivocal. However, to decide whether this vasoconstriction is "active" or merely "passive" (*due to the distensibility of* vessels), it is necessary to see how the pressures *have changed.* If, accompanying the increase in resistance, *the pressure either remained*

on the heart, so its calculation is not very important with regard to clinical cardiology. The big item of load is the *energy cost of maintaining tension in the heart muscle* A muscle requires energy expenditure (measured by its oxygen consumption), even if it remains the same length (isometric contraction) and so does no mechanical work at all. As in other muscles, the energy consumption is *proportional to the tension developed multiplied by the time it is maintained*, i e , $\int T\,dt$ The load on the heart is the sum of this factor and the rate of mechanical work. The *mechanical efficiency* of the heart is defined as the mechanical work over the total load. This is very low, because the tension-time integral is much greater than the external work, in most circumstances. *The total load on the heart is, therefore, determined*, not so much by the mechanical work of pumping the circulation, but by the arterial pressure that has to be developed, with the size of the heart (this determines the tension in the heart muscle), and by the total time during which the heart muscle is contracted (duration of systole) An increase in heart rate increases this time almost proportionately, and thus the *load on the heart is almost proportional to* arterial pressure × heart rate (Burton, 1957).

17. The Relation between Tension in Heart Muscle and Systolic Pressure. This has been greatly neglected The classical *law of Laplace* (1824) states that the pressure developed in a viscus will depend on the tension developed in its walls and upon their "curvatures" If the heart is dilated to twice the size, the tension in the *ventricular muscle will have to be at least* four times as great to produce the same systolic pressure The load on the heart [as above in (16)] will, therefore, be very much increased by cardiac dilatation, as well as by hypertension. A dilated heart is mechanically much less efficient

18. Noise in the Cardiovascular System. Flow in a tube is *streamlined* and *completely silent. If there is sound in the circulation, it* denotes a vibration, an instability of flow, or *turbulence* When steady driving pressures are applied to make fluid flow through a tube, turbulence is reached at a "critical velocity," which depends upon the radius of the tube r, the viscosity of the fluid η, and its density ρ, according to Reynolds' criterion,

$$V_c = K\frac{\eta}{\rho r} \qquad (K \text{ is dimensionless})$$

$$\text{Units: cm/sec} = K \times \frac{\text{poise}}{\text{Gm/ml} \times \text{cm}}$$

K is Reynolds' number, which is about 1,000. For pulsatile pressures, the critical velocity may be less. Using 1.2 cm for the radius of the aorta, and 0 035 for the blood viscosity η (relative viscosity 5), and 1.0 for its density,

$$V_c = \frac{1{,}000 \times 0.035}{1 \times 1} = 30 \text{ cm/sec}$$

A cardiac output of 5 liters/min (83 ml/min) with an aorta of radius 1.2 cm, i e , of area 4 cm^2, corresponds to a mean velocity of $^{83}/_4$, about 21 cm/sec. One would expect then to find turbulence, and to hear noises in the circulation during the height of systole in the aorta, but not at other times, or at any time in normal arteries or other vessels than the aorta In *heavy exercise*, Reynolds' criterion is reached in the aorta, even in diastole In pathologic narrowing of arteries, or with very high velocities through arteriovenous fistulas, there will be turbulence and noises (bruits, murmurs, etc.).

The *murmurs in children* after heavy exercise are due simply to their high cardiac output and consequent high velocity in the aorta, exceeding the criterion for turbulence, at times other than the opening and closure of the valves The *murmurs of chronic anemia* are also due to high cardiac output Similarly, in a patient otherwise normal but with an unusually narrow brachial artery, the disappearance of the sound in taking the blood pressure may not occur until very low cuff pressures are reached

19. Resistance to Flow. The usefulness of the concept of "resistance to flow" is *not* dependent on any set of assumptions as to normal viscosity, rigid tubes, etc , as many have imagined (any more than speaking of the price of an egg is invalid because that price varies according to the quantity of eggs purchased) The concept of resistance has intrinsic value without any need to refer to Poiseuille's or any other law

Resistance to flow is defined as the ratio of the driving pressure, ΔP, between any two points, and the flow that results,

$$R = \frac{\Delta P}{F}$$

7

The laws of the isolated heart

CHANDLER MC C. BROOKS

The heart is, of course, an indispensable organ, and just as the body is dependent upon its functions so the heart is dependent upon function of the other body organs. The heart requires a relatively constant environment of a very specific nature, and its ability to survive and maintain normal activities in "isolation" is merely relative; it can be isolated only from certain of the influences which normally act upon it.

THE ISOLATED HEART

Isolated, perfused hearts have been kept alive for very long periods, and *heart cells* in tissue culture can be and have been maintained for an indefinite period of time. Under such conditions of isolation, these heart cells and the myocardium contract and relax in a relatively normal fashion. They must, however, be supplied with oxygen and a variety of nutritional and other materials required by their metabolic processes (Chaps. 2 and 3). Further- [illegible] there are limits to the heart's toleration of changes in temperature, acid-base balance, metabolite concentrations, and other environmental impingements.

The heart will, however, continue to beat quite effectively in the absence of many of the normally present influences which integrate its level of activity with the ever-changing requirements of the body tissues for blood. The heart can be deprived of extrinsic nerves, the chemical mediators, and the hormones, which normally serve as controlling agencies, without loss of effectiveness of function and some of this organ's compensatory abilities. The practice of isolating the heart from many of the influences which modify its function has become common and has enabled physiologists and clinicians to learn much about the basic processes of its operation.

SPONTANEOUS ACTIVITY

One of the most striking characteristics of the isolated heart, and even of isolated heart cells, is that they continue to beat normally. This property of spontaneity of contraction is developed to a higher degree in some cardiac tissues than in others, but *the sinus, atrial, Purkinje,* and *ventricular tissues* all have a characteristic rhythm if supplied with normal amounts of oxygen, nutrients, and ions. The heart tends to follow the rhythm set by the most rapidly beating of its tissues, the sinus venosus in amphibia and reptiles, and the *sinoatrial (SA) node* in the mammalian heart. Domination by such a pacemaker under normal circumstances subjugates the tendency toward independence of beat origin in other portions of the myocardium. When local excitatory influences predominate or when conduction of the excitatory process from the normal pacemaker to other regions of the heart is blocked, then *ectopic foci of beat origin* may develop.

There was for some time a controversy as to whether the heart beat had a *neurogenic* or *myogenic* origin, but this problem was resolved by the observation that heart cells beat in tissue cultures in the absence of neurons. It is only in some invertebrates, *Limulus,* for example, that the heart is dependent upon a

constant or rose (which would tend to distend the vessels passively and lower the resistance), the observed constriction must have been "active." If, however, *the pressure fell*, the constriction may have been either passive or active, and only data on the degree of distensibility, i.e., the amount of passive change of resistance with pressure, will decide this point.

Conclusion. The fact that the living circulatory system is very complex is certainly no reason for failure to apply the simple physical laws that must apply to all systems, nor any excuse for the false impressions of the importance of the various factors that result when the application of physics is not quantitative.

from the pacemaker involves a transfer of charge and a current flow similar to that applied in electrical stimulation. It is interesting that the intrinsic excitatory process is several times stronger than it need be to excite adjacent tissue (Brooks et al., 1955); this is important in considering conduction and the origin of fibrillation (Brooks, 1956).

The resting membrane potentials and the excitability of various types of cardiac cells are quite similar. They are all affected in much the same fashion by drugs, neurally transmitted influences, and physical changes. Action potentials vary chiefly in their duration. The excitability and action potential form and duration are determined, of course, by the characteristics of the component elements. The chief differences in heart cells and in the tissues of the various chamber walls lie in the realm of the processes of repolarization and the recovery of excitability following a heart beat.

Figure 2-22 shows the repolarization of a ventricular cell and the recovery of excitability. It is now common knowledge that as a cell is excited and depolarizes, it becomes inexcitable until repolarization has occurred. Probably Fontana (1785) was the first to suggest the general concept of a *refractory period*, but Marey (1876) effectively introduced this idea. Carlson (1906) first employed the expressions "absolute refractory period" and "relative refractory period," thus emphasizing that excitability is recovered progressively.

The most recent studies have shown that recovery of excitability involves a little more than is implied in the statement that it is due to repolarization. Testing of the excitability of the heart throughout the cycle by applied stimuli reveals changes not predictable from even the intracellularly recorded action potential. Testing of the recovery of excitability of the heart using bipolar stimuli has shown that there is a period of *relative supernormality* after attainment of full repolarization. This initial supernormality (Fig. 2-22), has been called the *dip* because of its appearance on the strength-interval curve. It is in fact a period of supernormality to anodal stimuli, while the later or traditional supernormality is a cathodal supernormal period. Finally, it has been found that under certain conditions, recovery of excitability lags behind the repolarization processes (Brooks et al., 1955).

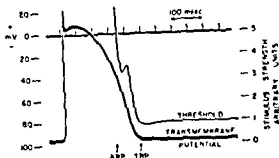


Fig. 2-22. The temporal relationship between phases of the intracellularly recorded ventricular cell action potential and the recovery of excitability. Note the dip and the supernormality indicated on the excitability recovery tracing.

One of the most puzzling features of the fluctuating excitability of the whole heart (Orias et al., 1950), and even of the heart cell (Hoffman and Kao, 1957), during this recovery phase is that in the dip area, the heart is not only more susceptible to anodal current (the "off" or "break" effect of anodal current flow) than it is to cathodal current, as throughout other intervals of the cycle, but there is actual anodal supernormality (Cranefield et al., 1956). It is quite probable that the greater effectiveness of anodal current flow during recovery is associated with its repolarizing action on the membrane. It may be that the membrane is repolarized before the intrinsic metabolic process (the ion exchange pump) has been reassembled or has recovered sufficiently to maintain the membrane in a stable state. One would not expect current flow which can transfer charge and aid in repolarization to participate necessarily in enzymatic readjustments. Another most interesting and important feature of this dip phase of the cardiac excitability cycle is that *the heart is abnormally susceptible to fibrillation during this interval* (Hoffman et al., 1955).

As the cardiac cycle is shortened by *acceleration of the heart*, the recovery of excitability and repolarization are also speeded up. The refractory period is shortened, as well as the period of diastole or maintained membrane polarization. Drugs, neural influences, epinephrine, acetylcholine, temperature change, also modify the recovery processes much more than they do the depolarization (rising phase of the action potential) and resting membrane potential. Some of these agencies affect the absolute

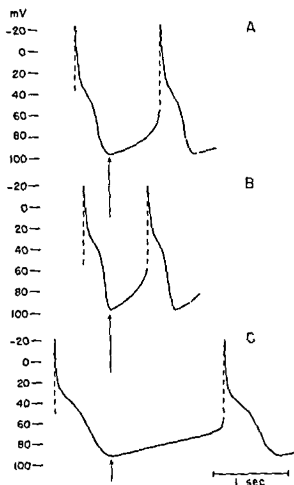


Fig. 2-21. *Action potentials recorded intracellularly from pacemaker tissue showing the prepotential, or spontaneous, depolarization. A Normal B During stimulation of cardioaccelerator nerves. C During vagus nerve stimulation Voltage scale refers to intracellularly recorded resting and action potentials (Redrawn from Weidmann, 1955)*

neural drive Just why cardiac and smooth muscles possess an intrinsic rhythmicity of action is still not fully understood, but the question of the origin of the heart beat has been dealt with in another chapter (Chap. 4). However, it suffices to say here that the isolated heart continues to beat because of an intrinsic excitatory process in its pacemaker The pacemaker cells, like all other cells of excitable tissue, possess a membrane which repolarizes after each excitation In all cells, after passage of the action potential, metabolic processes, described as the activity of an "ion exchange pump" (Hodgkin, 1951; Hodgkin and Huxley, 1952a, Shanes, 1955), remove the excess sodium ions which entered the cell as the regenerative process initiated the ionic flux on excitation, and permit or participate in the reestablishment of the normal extracellular-intracellular ion partition and membrane potential. Since the plasma or cell membrane is somewhat "leaky," this metabolic activity (activity of the pump) must continue if membrane polarization is to be sustained. These polarizing processes actually resist depolarizing influences Their ability to resist depolarization determines to a degree the threshold requirement for stimulation (Brooks et al, 1955).

It appears that in the pacemaker, or in all tissues which have assumed pacemaker activity, the membrane begins to depolarize spontaneously as soon as, or shortly after, repolarization *The pacemaker can therefore be thought of as a cell with abnormal instability of its membrane* These processes which repolarize, or, more specifically, the processes which tend to hold a membrane in a stable polarized state, are unable to counteract intrinsic tendencies to depolarize. It has been shown that nerve actions and chemicals which affect heart rate act by accelerating (epinephrine) or slowing (acetylcholine) the build-up of the prepotential which is the sign of progressive local depolarization in the pacemaker (Weidmann, 1955c). This is what can be said up to the present as to why the isolated heart continues to beat quite normally Figure 2-21 shows the pacemaker action potential and how it is affected by influences which accelerate and slow the heart

THE EXCITABILITY CYCLE AND REFRACTORINESS OF THE HEART

One of the major discoveries or concepts of biology is that living tissues possess *irritability* Irritability is the property of being excitable, or of being able to detect a stimulus and be so affected by it that a response is initiated. It has long been known that cardiac muscle, like skeletal muscle, smooth muscle, and nerve, can be stimulated in a variety of ways Local application of heat, cold, osmotic force, chemicals, pressure, etc, will cause an *extrasystole* The type of stimulus most commonly employed to estimate the excitability of a tissue is electrical current The quantity and duration of current flow can be so readily determined and controlled that practically all descriptions of excitability of a tissue are given in terms of strength-duration characteristics of effective electrical pulses. As a matter of fact, *the normal excitatory process which is transmitted*

from the pacemaker involves a transfer of charge and a current flow similar to that applied in electrical stimulation. It is interesting that the intrinsic excitatory process is several *times stronger* than it need be to excite adjacent tissue (Brooks et al., 1955); this is important in considering conduction and the origin of fibrillation (Brooks, 1956).

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The most recent studies have shown that recovery of excitability involves a little more than is implied in the statement that it is due to repolarization. Testing of the excitability of the heart throughout the cycle by applied stimuli reveals *changes not predictable* from even the intracellularly *recorded action potential*. Testing of the recovery of excitability of the heart using bipolar stimuli has shown that there is a period of *relative supernormality after attainment* of full repolarization. This initial supernormality (Fig. 2-22), has been called the *dip because of its appearance on the strength-interval curve*. It is in fact a *period* of supernormality to anodal stimuli, while the later or traditional *supernormality* is a cathodal supernormal period. Finally, it has been found that under *certain conditions*, recovery of excitability lags behind the *repolarization* processes (Brooks et al., 1955).

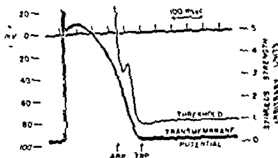


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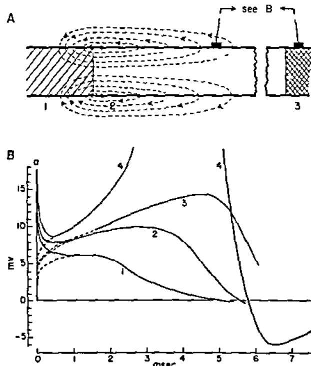


Fig. 2-23. Diagrams of electrotonic current spread along a fiber in advance of and causative to a transmitted depolarization. A, Recording of a transmitted depolarization, 1, the electrotonic current flow, 2, and an area of injury, 3, employed to permit monophasic recording of local responses, B-1, 2, 3, or local changes preceding a propagated action potential, B-4.

refractory period more than the relative, as though the chemicophysical processes of the terminal phases of repolarization and excitability recovery are more immutable than are the initial steps of the recovery processes

The isolated heart, as well as elements of isolated tissue containing only a few cells, shows excitability recovery curves, action potentials, etc., identical with those of hearts and cardiac cells in situ, as long as the required nutrients are provided and a normal ion balance is maintained

RESPONSE OF THE ISOLATED HEART

Every heart beat is the result of an electrical and mechanical response to the intrinsic stimulus generated in the heart's pacemaker The responses of the heart appear to be identical regardless of whether the reaction originates in a normal pacemaker or from an applied electrical or physicochemical stimulus of another type. In discussing this response, or the heart's contraction, it is customary to discuss separately the electrical response, conduction, and contraction. *It should be remembered, however, that these are closely interrelated, though somewhat independently variable, processes.*

The Electrical Response. When a stimulus is applied to a cell membrane, the resting potential need be reduced only to a critical level to produce excitation. For example, the resting potential of a heart cell is approximately 90 mv. If the applied cathodal current is sufficient to reduce this potential to only 70 mv, the membrane becomes unstable and a regenerative process (a self-sustaining reaction) is initiated which completes the depolarization. This intrinsic depolarization process can be considered to be an active response. Once this depolarization has occurred, a segment of depolarized membrane surrounded by normally polarized membrane exists in the cell or myocardium.

Figure 2-23 shows how the proximity of a negatively charged surface to positively charged normal membrane surfaces sets up a local current flow. If the depolarized area is very small or the surrounding membrane very inexcitable or very stable (as when cocaine or some other of the antifibrillatory drugs is used—see Weidmann, 1955c), only a local response occurs The area of depolarization does not expand appreciably and eventually is again polarized Accommodation in the normal membrane may also tend to confine the effects of a stimulus or injury. If, on the other hand, the normal membrane is of normal excitability and the original stimulus does depolarize a sufficient area of membrane, then the local eddy currents, as they flow through the junctional membrane, reduce its resting potential to a critical level and touch off the regenerative process there. Thus, propagation of the excitatory process, or conduction, occurs

Conduction. One of the first major contributions to cardiac physiology was the discovery of the *all-or-none law* by Bowditch (1871) while he was a student of Ludwig at Leipzig This generalization or law, briefly stated, is that *when the heart is stimulated, it contracts as a whole or not at all* Now that the mechanism of propagation of the excitatory process and something of the anatomy of heart muscle are known, there appears to be nothing mysterious about this law. The myocardium is a *syncytium*, therefore there are no major barriers to propagation of the excitatory process

throughout the heart. Since excitation and propagation thereof are intrinsic processes, merely touched off by the initial stimulus, there is no reason for equating the strength of this initial stimulus with the magnitude of the response. The all-or-none law does not indicate that the strength of a cardiac contraction must *always* be the same, nor that stimuli must *always* evoke a propagated electrical response and contraction. The conducted excitatory process depolarizes the membrane, and, as a result, a contractile process occurs which is of a magnitude permitted by conditions prevailing in the heart and not determined by the initial excitation procedures.

Conduction is initiated by the electrotonic current flow originating from the adjacency of a sink (a depolarized area) and a source (a polarized membrane). This current flow is detectable several millimeters in advance of the boundary between depolarized and polarized tissue. Since voltage differences are such that the intensity of current is greater than need be to excite, it retains sufficient potency to stimulate at a distance. Therefore electrotonic current flow can spread across narrow gaps (*Wedensky facilitation*) and depressed cells, possibly exciting hyperexcitable cells at a distance. The importance of this for the possible origin of fibrillation needs no emphasis (Brooks, 1956).

Later work (Hoffman and Kao, 1957) has emphasized some other points concerning conduction of the excitatory process. In the first place, there is junctional tissue between the Purkinje fibers and undifferentiated ventricular muscle. It is conceivable that drugs might confine activity or block conduction by action on these susceptible junctional connections. In the second place, Purkinje fibers require longer to repolarize than does ventricular muscle. It is therefore possible to initiate an impulse in a papillary muscle which will reach the Purkinje fibers during the late stages of their refractoriness. It has thus been shown that *the intrinsic excitatory process propagated through the myocardium is sufficiently strong to stimulate refractory heart fibers.* The propagated impulse can activate all portions of the normal heart in situ or normal isolated heart. Study of excitation of individual contractile muscle myofibrils has led to the conclusion that a wave of depolarization is transmitted into the interior of the fiber along a transverse membrane, the Z line or membrane, and thus *activator* is released in the interior of the fiber. This activator initiates the contraction (Huxley and Taylor, 1955).

Contraction. In considering contraction of cardiac muscle, some general problems as well as some specific ones are encountered. The first general problem is: What is the nature of contraction, and how does depolarization of the cell membrane initiate contraction?

The first statements which can be made are that though propagated depolarization of the membrane of muscle cells touches off the contraction, the two processes are separable. *Contraction without depolarization occurs on exposure to high pressures.* Following excitation, the ability of cells to propagate excitation is recovered faster than their ability to contract. Under abnormal conditions produced by drug action, etc., *an impulse can be propagated through the myocardium without arousal of contraction.* Digitalis is known to increase strength of cardiac contraction in concentrations which do not appreciably change the amplitude or duration of the action potential.

Contracture of a muscle is a shortening not preceded by conducted electrical changes. Intravenously injected acetylcholine has long been known to cause contracture of skeletal muscle fibers, especially when they are denervated. Hajdu (1953), in discussing the role of potassium ion in contracture, points out that a decrease in intracellular K^+ favors the association of actomyosin, while a decrease in extracellular K^+ diminishes this association. Contracture will result if the equilibrium between the two (intra- and extracellular K^+) is disturbed. The membrane potential is of importance too. This same author found evidence which indicated that in the presence of an increase of total ionic content ($Na^+ + K^+$), a higher membrane potential is necessary to prevent association of actomyosin and thus contracture. Further elucidation of this problem appears to depend upon a better understanding of the contractile process in muscle. It is certain, however, that changes in ion concentration modify contractility.

It is generally conceded that chemical and physical processes involved in contraction must be much the same for striated muscle whether cardiac or skeletal (Szent-Gyorgyi, 1956). In recent years, there have been considerable ad-

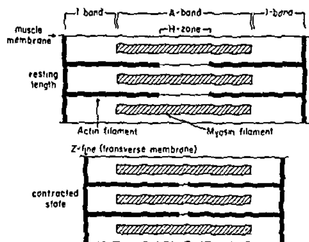


Fig. 2-24. Diagrammatic summary of one concept of the occurrences during muscle contraction.

vances in the knowledge and understanding of muscular contraction because of biophysical and biochemical studies of purified muscle proteins and investigation of molecular structure of muscle and the change in structure during contraction (Huxley, 1956). In dealing with this subject, the anatomic properties of striated muscle will be considered first (Fig. 2-24), and then the biochemical evidence

It has become possible to hazard an explanation of contraction and the effects of muscle stretch Several lines of evidence suggest that the high refractive index and the birefringence of the A bands in striated muscle are due to the presence there of thick (100 A) rodlets of myosin oriented parallel to the long axis of the muscle fiber These rodlets and the A bands do not change in length when a fiber is stretched or when it contracts Parallel to these rodlets, but running from the H-zone border of the A band to the Z line or membrane of the more translucent I band, are thinner (50 A) filaments of actin Contraction is brought about by some mechanism which causes these filaments of two different types to slide past each other, and only the I band is reduced in length In normal contraction, reduction of the I bands permits shortening of a fiber to about 65 per cent of its initial length In isometric contraction, in which the muscle is not allowed to change in length, neither the A nor I bands shorten. The H zone also shortens during contraction When a fiber is stretched, it (the H zone), as well as the I band, lengthens The change in the H zone permits the two (actin and myosin) fibers to slip past each other without a change in their length, as though a bonding were being shortened. If the shortening is very great, there appears to be a crumpling up of one or both array of fibers, or of both arrays, at their ends, and the H zone becomes more dense. These are the structural changes visualized as occurring during muscle contraction

The biochemical evidence indicates that a combination can occur between the actin and myosin known to be present in muscle fibers This tendency to combine is modified by the presence of *adenosine triphosphate (ATP)*. Myosin is an ezyme capable of dephosphorylation of ATP if activator is present. Presumably, when activator is released by membrane depolarization, ATP is dephosphorylized and energy is released for contraction. An interaction between myosin, actin, and ATP takes place which draws the array of actin filaments into the array of myosin filaments, and the muscle shortens When ATP breakdown ceases, the interaction between myosin and actin stops Furthermore, the inactivated ATP has the effect of breaking the links or bonds between the two filament types, and the muscle becomes extensible. If the ATP is washed out, however, the myosin and actin filaments remain locked together and the fiber is locked in a shortened length (*state of contracture*) The manner in which these bonds, or cross linkages, work is somewhat complex and requires further study. It appears that in isometric contraction, more linkages can form and thus more tension can be generated than if sliding of the filaments is permitted

The nature of the "activator" which is released from the depolarized membrane or is permitted to enter the cell by this depolarization is still not known Until more evidence is provided, *the activator can be thought of as the process of membrane depolarization* Activation is associated with the Na^+ and K^+ ion flux, but until further progress can be made, it will be necessary to add to this knowledge more or less unexplained observations. Examples of these are that certain steroids affect contraction by modifying membrane permeability, that there is a decline in activity associated with an increase of internal chloride, that maximum tensions can be developed at certain temperatures, that various nutrient materials have a greater isotropic effect at one temperature than at another, etc (Feigen, 1956). Un-

til these matters can be resolved, known properties must be used to explain functional behavior.

TONUS

Frequent reference is made to the *tonus of the heart* The term "tonus" has many uses Sometimes it is employed to describe a persistent moderate degree of *activity in* a tissue According to Starling, what is usually called tonus of the heart is synonymous with *its physiologic condition* By this usage, a heart is said to have a high tonus if it is in good condition and if it empties itself almost completely at each systole A fatigued heart, or one which retains residual blood at the end of a systole, is said to have a low tonus. Wiggers, on the other hand, uses the term tonus to describe *distensibility.* Resistance to stretch or distention is thus indicative of good tonus By modern theory, the presence of unactivated ATP, its quantity, and the factors modifying its action on the myosin-actin linkage determine the extensibility of muscle, resistance to distention, and thus cardiac tonus, if Wiggers's usage of the term is followed.

TETANUS

Another of the questions frequently asked concerning the heart is "Can summation of contraction and tetanus occur in the heart?" A qualified *negative answer* can be given in both instances The heart differs from skeletal muscle in this respect Skeletal muscle must be able to remain in a contracted state in order to permit maintenance of posture The heart is a pump which must regularly fill and empty The longer refractory period of cardiac muscle and its persistence during the phase of muscle contraction and relaxation prevents easy tetanization The early recovery of excitability does permit stimulation of the heart and another partial contraction before relaxation *is complete. Summation can occur, and the heart, therefore, can be tetanized to some degree if definition of this term requires only a new contraction before complete relaxation* Suprathreshold stimuli must usually be used, however, and it can be said with certainty that though a degree of tetanization of the isolated or exposed *in situ* heart can be produced in the laboratory, there is no normal mechanism for tetanizing the heart in situ similar to that which customarily operates to sustain contraction in skeletal muscles.

STAIRCASE

It has already been mentioned that digitalis-like substances can modify the strength of contraction by some still unknown action It was early observed also that when a quiescent heart is first induced to beat, the second, third, and fourth, or more, beats are larger than the first (Cattell and Gold, 1941) This gives a stepwise increase in magnitude or force of contraction which is referred to as treppe, or "staircase." It is easy to say that this is the result of "warming-up" and reduction of intrinsic resistance, a change in viscosity due to liberation of metabolites, etc, but harder to prove In a study of treppe by Hajdu and Szent-Györgyi (Szent-Györgyi, 1953), it is assumed that sufficient potassium ion is accumulated in resting heart cells to depress the association between actin and myosin A series of contractions is accompanied by a reduction in intracellular K^+, and a condition more favorable to the association of actin and myosin develops The changes in internal potassium and sodium brought about by a variety of conditions known to affect treppe were determined. The height of developed tension was found to parallel loss of K^+ from the heart. Treppe, *however, is* again a phenomenon of the laboratory, normally beating hearts are not in a state of rest a sufficient time to permit a treppe-like change in contraction to occur on reactivation

POTENTIATION

Another interesting phenomenon which has been recognized for some time (Brooks et al, 1955) is potentiation of the strength of the beat following an interpolated extrasystole or a series of extrasystoles When a propagated impulse unassociated with a full mechanical response traverses the heart, it produces some change that modifies the next mechanical response, which occurs even though it *may* be delayed for several minutes A propagated wave of membrane depolarization, which occurs too early in the recovery phase following a preceding beat to have permitted full recovery of the contractile process, may evoke only a minimal or no change in tension There is, however, a residual effect, inversely proportional to the size of the mechanical extrasystole, which is

transferred to the next contraction. Figure 2-25 illustrates the occurrence of the phenomenon. Apparently the transmitted membrane depolarization, by reducing the intracellular K+ concentration or by some other effect, creates a condition more favorable for contraction. This example of circumstances favoring mechanical response of the myocardium can be seen in strips of tissue and in the intact in situ heart following an early interpolated extrasystole. Since no greater filling of the ventricle need *occur and no increase in fiber length is entailed in the production of this phenomenon, it should not be confused with the operation of Starling's law of the heart.*

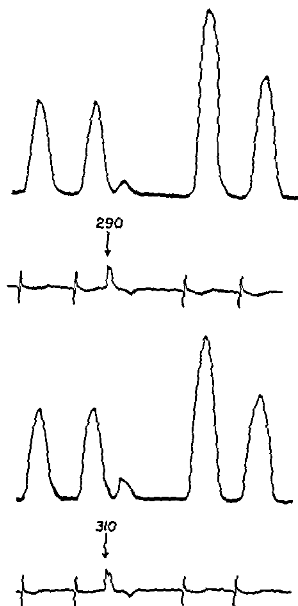


Fig. 2-25. Tracings of the electrograms and myograms of contracting ventricular tissue showing the electrical and mechanical responses to very early extrasystole. Note that the normally induced beats following the premature extrasystoles show augmented mechanical reactions.

LAW OF THE HEART

Compensatory activity of the heart and an increase in cardiac output to meet a greater body need for oxygen or other blood constituents are effected by *an increase in rate, an increase in stroke volume, or both.* Both this increase in rate and volume output per beat may result from *an increase in venous return* or *the action of physicochemical agents* directly on the myocardium. The isolated heart is *not* subject to the *Bainbridge (cardiac accelerator) reflex*, nor to diminution of *the depressor reflex* originating from the stretch receptors in the carotid sinus and arch of the aorta, nor to the direct action of *sympathetic nerves* or *blood-borne epinephrine*. An increased rate of filling of the perfused heart and an increased stretch (fiber length increase) on isolated cardiac muscle *does* increase the strength of contraction because of preceding increase in diastolic volume caused by an augmented venous return. This is the phenomenon described as Starling's law of the heart.

There has been a great deal of discussion of the validity of Starling's law and of the effect of initial, diastolic, or resting fiber length on the tensions developed by the contracting fiber. It may be the initial tension rather than the fiber length which determines the strength of contraction, but under ordinary circumstances, when a fiber is lengthened tension is increased. Fibers in situ are always subject to some tension, and this tension and fiber length may be more nearly optimal than in a Starling heart-lung preparation. It has also been found that the nonisolated heart may increase the strength of its contraction because of nervous or humoral effects on the heart rather than because of an increase in venous pressure and venous return. The evidence that factors other than fiber length, initial tension, or both may modify the strength of contraction should not be construed as a denial of the fundamental importance of Starling's law of the heart. Increased filling within limits does increase the strength of cardiac contraction even when the heart is isolated.

PHYSICOCHEMICAL INFLUENCES ON THE ISOLATED HEART

Isolation of the heart from the body does not desensitize this organ to hormones, changes in ion concentration, drugs, heat or cold, and the action of other agents. As a matter of fact, *denervation causes the myocardium to become much more sensitive to adrenergic and cholinergic substances,* although a few days (3 to 7) are required for development of maximal sensitivity following denervation

Cocaine, procaine, quinidine, etc., act by stabilizing the cardiac cell membrane *Acetylcholine* has been reported to hyperpolarize the membrane, but its effect on resting potential is minimal It does tend to increase cardiac excitability, but its most marked effect on the heart cell is to greatly hasten repolarization, and it may even abolish any sign of a plateau in the transmembrane action potential Its depressant effect on the heart is due to its action on the pacemaker. *Epinephrine* and similar substances strengthen the contraction of isolated cardiac tissue, initially increase excitability, and hasten repolarization In the case of acetylcholine, epinephrine, and norepinephrine, there is a reversal of effect (Brooks et al., 1955) *With* respect to these hormones, mediators, and drugs, there appears to be no cardiac action peculiar to the *isolated heart*

The importance of *specific inorganic ions* to heart function was initially realized because of work on isolated perfused hearts Ringer in 1883 found that simple saline (NaCl) perfusions would not enable the frog heart to continue beating for any length of time He found that $CaCl_2$, when added to the NaCl, enabled the heart to resume its beat, but a state of continuous contraction eventuated *When appropriate amounts of* KCl were next added, *the heart* was able to beat nearly indefinitely Other trace substances, buffers, and nutrient elements were eventually found to improve the performance of the heart. Now a *variety of* formulas for mammalian and submammalian physiologic *saline solutions* are available

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pr... maintained in perfusing fluids by choline chloride, a marked decrease in extracellular Na^+ results in a slowing of impulse formation, a decrease in conduction velocity, AV dissociation, a decrease both in the rate of rise and the magnitude of the transmembrane action potential, and eventually in a complete loss of excitability Lithium can substitute for extracellular Na^+ *to a limited extent.* The changes in Na^+ tolerated by *the total organism,* however, have little effect on cardiac excitability or response.

2. *Magnesium, Strontium, and Barium.* Abnormalities in cardiac function resulting directly from alteration of blood magnesium concentration are not encountered, and even in perfused isolated tissues such change has little effect. However, when the concentration of calcium is decreased, Mg^{++} becomes more effective Elevation of Mg^{++} then decreases the duration of the transmembrane action potential A reduction in both Ca^{++} and Mg^{++} causes a prolongation of the action potential, the plateau phase of the ventricular cell transmembrane action potential may be prolonged from a normal duration of 100 to 200 msec to as much as several seconds Strontium also may act like Ca^{++} to some degree, but when it is added to a Ca^{++}*-poor perfusing fluid, the* action potential shows a change similar to that induced by complete Ca^{++} deprivation This suggests that the Sr^{++} displaced the remaining calcium Barium prolongs the ventricular action potential even in the presence of normal Ca^{++} levels Barium is of course a powerful myocardial stimulant and may cause systolic cardiac arrest Although it lacks a specific effect on the conduction system, it has been used in cases of heart block because of its accelerator and digitalis-like action, which alleviates distress, if not the heart block (*Goodman and Gilman, 1955*) *The only other observations* which should be noted are that Mg^{++} is *thought* to depress impulse production in ectopic centers, but of course central nervous system depressant action is much more prominent

3. *Calcium.* Calcium is essential to normal function of the nervous system and to the heart, as well as to skeletal development The body requirement is 10 *mg* daily The resting membrane potential of the heart cell is little affected by a fourfold increase in Ca^{++} or a de-

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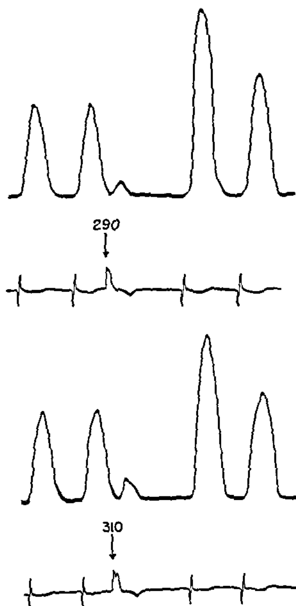


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crease to one-quarter the usual concentration. A high concentration tends to stabilize or increase membrane potential and decrease excitability, because resting potential must be lowered more than usual before a regenerative depolarization procedure begins. Low Ca^{++} increases the excitability of the heart. When Ca^{++} level is only about one-tenth normal, pacemaker action is augmented and the rate of fiber depolarization is increased. Ectopic pacemakers develop. *The atria are much more sensitive to changes in Ca^{++} than are the ventricles or the specialized conducting tissues.* High calcium speeds the early phases of repolarization in the auricular fiber, but low Ca^{++} causes it to develop a plateau phase similar to that of ventricular cells. Ca^{++} has an effect on Na^{+} flux through the membrane during excitation; low Ca^{++} decreases sodium permeability, while high Ca^{++} has the opposite effect Very high and low Ca^{++} levels tend to favor development of fibrillation, but the mechanism of action is different. The K^{+}-Ca^{++} balance is important The depolarizing actions of K^{+} are opposed by Ca^{++}, *hence the use of K^{+} to stop fibrillation by its depolarizing action and the subsequent use of Ca^{++} to restore normal function.* The effects of Ca^{++} excess on the P-R and Q-T intervals of the electrocardiogram are well known. The delay in conduction may be due in part (but not entirely) to acetylcholine liberation when the vagi are intact. Calcium modifies muscle contraction also. In the absence of Ca^{++}, the heart stops beating as though an excess of K^{+} had been given *An excess of Ca^{++} causes "calcium rigor" and thus a systolic arrest*

*4. **Potassium.*** Potassium is the chief cation of the intracellular compartment In the absence of K^{+} the perfused heart stops beating in systole. When there is excess extracellular K^{+}, the plasma membrane depolarizes and remains depolarized, the heart beat ceases in diastole or at full relaxation, and the tissue is excitable A lowering of membrane potential by a slight increase in K^{+}, of course, increases excitability because of instability of the membrane Lowering extracellular K^{+}, especially if Ca^{++} is at a low normal level, results in an enhanced spontaneous rhythmicity and even development of ectopic pacemakers Raising K^{+} concentration enough to render the membrane somewhat unstable also enhances rhythmicity, but higher concentrations cause a loss of pacemaker action, although pacemaker tissues are less susceptible to changes in K^{+} than atrial and even ventricular muscle. Elevated K^{+} reduces the rate of rise of the action potential, causes a shortening of its duration, abolishes the overshoot, and decreases the velocity of impulse propagation. *These effects can be ascribed to the lowering of the membrane potential.* Atrioventricular dissociation occurs in the presence of high serum potassium. An AV block, a reduction of the T-wave amplitude, and a prolonged QRS complex are revealed by the electrocardiogram. A good deal has already been said of the effect of the K^{+} on muscle contraction and myosin-actin combination. In considering the effects of K^{+} ion concentration change, the potassium-calcium balance must be taken into account Calcium ion can be employed to counteract the effects of K^{+}, but the interrelationship is not altogether simple

SUMMARY

The isolated heart contains a high degree of autonomy It can continue to function as a pump in complete isolation Neural and hormonal influences merely modify its activity to conform to body requirements, but even in this respect, the heart has an intrinsic ability. When more blood is returned to it, more blood is pumped out and a higher head of pressure develops. A supply of oxygen and nutrients is required, but aside from this, shifts in ion concentrations seem to have the most profound effect on cardiac function This is probably because the maintenance of specific ion partitions is required for maintenance of membrane potential, for ion flux in excitation, and for propagation of the excitatory process Ions may serve to activate the processes involved in muscle contraction, if not, they at least influence these reactions to a significant degree Much that is known of the process of excitation and contraction has been learned from studies of the isolated heart and cardiac tissues

8

The heart as a pump

CARL J. WIGGERS

The heart is a double-force pump designed to transfer venous blood under low pressure to the distributing arteries in sufficient quantities for the needs of the tissues and under sufficient pressure to enable its return to the right heart. It is a remarkable pump in many respects. It supplies its own spark and fuel, it maintains equal discharges of the two ventricles, and it automatically adapts its stroke volume to the heart rate and to the volume of venous return.

THE STRUCTURAL DESIGN

From a mechanical standpoint the *left ventricle* constitutes the muscular foundation around which the other chambers of the heart are built (Fig 2-26A). It is a conical, thick, muscular structure enclosing a cylindrical cavity with a conoid lower end. The thinner-walled *right ventricle* is, as it were, fastened anteriorly and laterally to the convex side of the left ventricular cone. Its cavity may be described as a crescentic pocket which provides a larger internal surface area for any given volume than the cylinder of the left ventricle.

The two *atria* rest upon the bases of their corresponding ventricles, the right occupying a more anterior, and the left a more posterior position. *Both atria are pulled downward and*

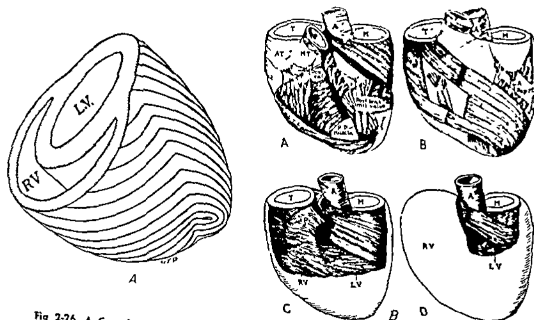


Fig 2-26 A Cone shaped left ventricle, *LV*, as basic structure of the heart with crescentic pocket of right ventricle, *RV*. B Muscular scrolls of the ventricles. A, Superficial bulbospiral fibers; *B*, superficial sinospiral fibers, C, deep sinospiral fibers, D, deep bulbospiral fibers. (*Rearranged after Robb and Robb, Am Heart J, 1942*)

stretched as the ventricular base descends during systole. This is evident both in myographic records of atrial contraction and as an abrupt fall of intraatrial and venous pressures. This causes the systolic collapse of veins in the lower neck.

ATRIAL MUSCULATURE AND CONTRACTION

The atrial musculature is arranged in thin sheets of fibers radiating from the AV ring. Two systems have been described: a superficial one, common to the two chambers and encircling them posteriorly; another independent for each atrium, with fibers arranged more or less at right angles. Impulses arising in the SA node spread radially over these fibers or, as Rijlant believes, over an undifferentiated stratum on the endocardial surface. The slow progression of the excitation wave induces a succession of fractionate contractions, giving atrial systole the appearance of a peristaltic wave in slow-motion films The spread of excitation is, indeed, so slow that the portions of muscle more proximal to the pacemaker start to relax before more distal fractions commence their contractions Lengthening of the atria begins as soon as the number of relaxing fibers exceeds that of the still contracting ones. Therefore, the period during which an atrium shortens, i e , its systole, is somewhat less than the time that all fractions continue to contract Such a summation of contractions is obviously not designed for development of much force

The vigor of atrial contractions is reduced in two ways by action of the *vagus nerves*, by slowing of conduction and by reduction in amplitude of fractionate contractions The *accelerator nerves* and *adrenergic agents* have an opposite effect.

The two atria of dogs differ in their pressure/volume relations, i.e , they display appreciably different volume-elasticity coefficients. In brief, *an equal increase in volume causes a greater rise of cavity pressure in the left atrium than in the right* (Little).

VENTRICULAR MUSCULATURE AND CONTRACTION

While the two ventricles are separate, physically and functionally, they have, for the most part, a common musculature. According to the descriptions of Mall, Robb, and others, three groups of common fibers, illustrated in Fig 2-26B, are distinguishable. These are (1) the superficial sinospiral, (2) the superficial bulbospiral, and (3) the deep sinospiral fibers In addition, a cuff of deep bulbospiral fibers surrounds the base of the left ventricle and the root of the aorta.

Electromyographic as well as myographic evidence indicates that *all parts of the ventricular surface contract within 0 02 sec.* Hence, it is a fair assumption that the entire ventricular musculature begins to contract almost, though not quite, synchronously. As a result of the uniform and powerful start of contractions, the ventricles become more globular. However, the mechanical stretch of the superficial fibers thus induced cannot immediately be overcome by their contraction, and, as a result, they lengthen briefly. According to Rushmer (1956), *the transverse diameter of the left ventricular cavity also increases before ejection starts.*

During ejection, all the external diameters of the ventricle decrease; *the base descends while the apex remains relatively stationary.* The furrow separating the two ventricles deepens, and, according to most descriptions, the ventricles rotate to the right, thus giving a more frontal exposure to the left ventricle On palpation, one experiences not only a sensation of great stiffening but also one of twisting The extent to which the base descends depends both on the aortic pressure, against which blood is ejected, and on the volume of the ventricle A well-filled heart apparently expels its blood chiefly by decrease in transverse diameters, a small and rapidly beating one appears to eject its blood by descent of the ventricular base.

According to Rushmer (1956), the reduction of the left ventricular cavity during systole involves only a slight decrease in length but chiefly a reduction in its transverse diameter. The cavity of the right ventricle is reduced somewhat by the increasing convexity of the septum but chiefly by an inward pull of the external wall toward the septal wall. Reduction in volume of the ventricular cavities is materially aided by their irregular internal surfaces and by the presence of the trabeculae carneae and papillary muscles However, it is now the consensus that a considerable, though variable, residual volume remains at the end of ejection under normal physiologic condi-

tions[1] In human hearts, Bing et al. (1951) found a range of residual volumes of the right ventricle between 23 and 160 ml (average = 89 ml).

In the left ventricle, blood enters and leaves by essentially the same pathway, but in the right ventricle there are definite *outflow* and *inflow tracts* which form an angle of approximately 90°.

FUNCTIONAL SIGNIFICANCE OF THE ARCHITECTURAL ARRANGEMENT OF THE VENTRICULAR MUSCULATURE

It is highly probable that the pattern of muscular bands (Fig. 2-26B) is significant in expelling blood with an economy of energy expenditure under different conditions However, the part that different muscle bands play in the mechanism of ejection has been differently interpreted and in many respects remains obscure The spiral arrangement of muscles led Mall to the inference that blood is virtually "wrung out of the ventricles by their twisting action", but this appears inconsistent with recorded changes in internal diameters of the left ventricle Rushmer (1956) therefore favors the view that the deep circular muscles initiate expulsion, and the surface layers operate toward its end He also believes that the rotation of the heart is small in the closed chest Interpretations are complicated, of course, by interactions of the various *muscle bands*, as they pull in different directions from different fixation points This produces stresses which tend to neutralize forces of contraction Indeed, the total force developed by contraction at any moment is a resultant of multiple vectors

From a mechanical standpoint, *shortening of a muscle* is most effective when one end is fixed and the other mobile Anatomists have suggested that the fibrous ring at the base of the heart, from which most of the muscle bands arise, may constitute a point of fixation However, since the base of the ventricles descends during systole, this fibrous skeleton can provide only a secondary anchorage It has been suggested that contraction of the superficial sinospiral fibers not merely strengthens the apical wall but causes the apex to become a stabilized region of muscular pull However, the superficial fibers begin to contract slightly later than the deeper scrolls There is more reason to regard the septum as a rigid axis around which other muscles contract it is the thickest muscular structure; it is centrally placed and the earliest to be excited. The septum shortens very little, contracts nearly isometrically, and so forms a stiff structure. The fact that, under comparable hemodynamic conditions, ventricular excitation from any ectopic focus results in less effective contraction, is difficult to explain on any other basis than that primary fixation of the septum is important in order to obtain a full effect of muscular contraction.

[1] Among the earliest evidence for existence of a residual volume was that of Chauveau and Favre (1856), who reported that a cavity could be palpated by a finger thrust through the ventricular apex of the horse, a favorite experimental animal of that period.

THE CARDIAC VALVES AND THEIR ACTION

The efficiency of the cardiac pump is materially enhanced by valves placed at the AV ostiums and at the roots of the pulmonary artery and aorta.

The AV [illegible] into two major triangular flaps on the left side (*mitral*, or bicuspid, valve) and into three similar flaps on the right side (tricuspid valve). The valve leaflets are thicker and contain a few muscle fibers at their origins but are thin and elastic at their free margins, which come into apposition on closure To the ventricular surfaces of the valves, are attached the *chordae tendineae*, arising from the papillary muscles They serve to tense and restrain the leaflets

The semilunar valves consist of three crescentic pockets attached to the walls of the aorta and pulmonary artery These pockets always contain blood, thus keeping them away from the walls. On closure, the free sides of these cusps are brought into apposition, from the ventricular side they appear as small bulging domes with a Y-shaped line of closure in the center

The movements of the mitral valve leaflets and the forces concerned in their closure have been derived by application of hydraulic principles, from observations and recordings of their movements in excised and perfused hearts, by their observation in hearts whose left ventricle had been opened, and by cinefluorographic ob-

servation of cardiac valves in the closed chest (Rushmer et al.).

A sensible integration of information obtained by these varied methodologies makes possible a fairly good picture of the mechanism of their closure. It is of primary importance that the valve leaflets are very light and have about the same specific gravity as the viscid blood; hence *they float* with the slightest directional shifts in the blood stream. Since pressure curves to be presently analyzed indicate that *abrupt shifts* in the stream take place shortly after onset and offset of systole, this probably constitutes the prepotent force concerned in *their closure and opening. However, there are still investigators who believe that the mitral* leaflets are effectively closed toward the end of atrial systole. Various mechanisms have been suggested as operative in causing such presystolic closure. These include (1) the formation of eddy currents, (2) a suction created by the breaking of a jet, and (3) sudden tensing of the *chordae tendineae* by lengthening of the chamber through the atrial increment of filling However, the force of atrial contraction is too small, and the interval between the termination of atrial systole and the beginning of ventricular systole too long, to make such forces very effective It is more probable, as Dean found in perfused hearts, that these forces can at most float the valves toward a position of closure. However, the valves would spread apart again unless the A_s–V_s interval is relatively short. Hence, the best evidence still supports the view that valve leaflets do not come into apposition until shortly after the onset of ventricular contraction. In addition to these mechanisms of closure, *the contraction of muscle bands encircling the valvular orifices reduces the size of the latter,* a mechanism that may be considered a factor of safety in minimizing leakage of valves that have become sclerotic, calcified, or deformed as a result of disease

Owing to the force with which blood is ejected, it is highly probable that the semilunar valves approximate somewhat during systolic ejection, as can be demonstrated in excised hearts. This may be because of the formation of eddy currents which, in the aorta, is increased by the development of positive pressure in *the sinuses of* Valsalva, owing to a brisk backflow from the *coronary arteries* The valve closes abruptly at the very onset of diastole because of a pressure difference between the two sides of the leaflets, created by the sharp decline of intraventricular pressure.

PRESSURE AND VOLUME CHANGES IN THE HEART AND LARGE VESSELS

By virtue of its muscular contraction, the human left ventricle ejects about 70 ml of blood against an aortic pressure of 70 mm or more within 0.25 sec. The ventricle then refills from the left atrium in 0 45 sec or less The cardiodynamic mechanisms concerned in such rapid filling and emptying have been elucidated by accurately recorded pressure and volume *curves from the dog heart, and deductions thus* drawn have been substantiated from human subjects through the application of more recently developed catheterization techniques.

The rapid changes in intracardiac and vascular pressures can be inscribed (both in man and animals) by adequate pressure recorders connected by rigid tubing with trochars that pierce the walls (Fig 2-27A) or by catheters inserted into the cavities via superficial vessels The changes of ventricular volume can be recorded in dogs by enclosing the ventricles up to the AV groove in a cardiometer connected to a volume recorder This can also be done with an intact pericardium (Fig 2-27B). This form of registration, of course, represents the changes in combined volumes of the two ventricles plus changes in blood volumes in the coronary vessels, facts that must be *taken into* consideration in interpretations. Katz and Katz have designed a preparation in which changes in left ventricular volume can be registered alone

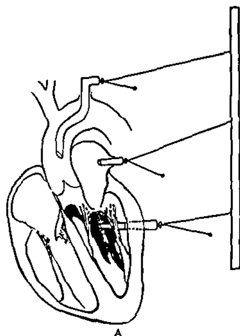
Simultaneous records obtained by these methods, when reduced to common ordinate values, can be superimposed (Fig. 2-28) and related to such events as the heart sounds and the deflections of a standard electrocardiogram.

Since the translation of pressure pulses into mental pictures has become an inescapable requirement in the present era of cardiac catheterization, it is necessary to analyze them in greater detail.

THE SEQUENTIAL PHASES OF THE CARDIAC CYCLE

The terminology suggested by the author (1921) *to designate the successive* events of the cardiac cycle has apparently gained general

acceptance As indicated in Fig. 2-28, ventricular systole commences with the initial rise of intraventricular pressure at A, and ends with cessation of all contractions at F. Diastole starts at this point (F) and continues until the next systole (A) These *periods* of systole and diastole are further subdivided into the following *phases* isometric contraction (A–C), maximum ejection (C–D), reduced ejection (D–F), protodiastole (F–G), isometric relaxation (G–H), rapid ventricular filling (H–I), diastasis (I–J), and atrial contraction (J–K)



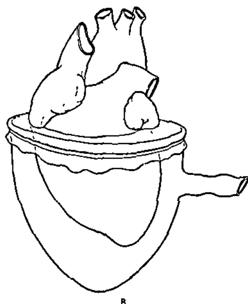


Fig 2-27 A Principle of registration of pressure pulses from aorta, left atrium, and left ventricle of dogs by optical manometers B. Application of cardiometer for registration of ventricular volume curves

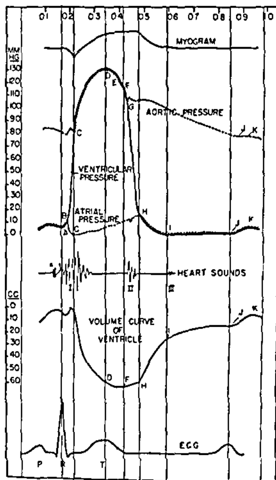


Fig 2-28 Correlation of left ventricular, aortic, and left atrial pressure pulses with surface myogram of ventricle, heart sounds, and ECG. (*After Wiggers. Circulatory Dynamics, Grune and Stratton*)

Isometric Contraction. This phase of rising tension (*Anspannungszeit*) lasts for only 0 05 sec or so, but important events preparatory to ejection are taking place At the end of a previous diastole, the left ventricle was distended under a few millimeters of mercury of pressure designated as the *end-diastolic pressure* Since this also represents the pressure under which contraction commences, it is also called the *initial tension* During the rise of the R deflection of a standard ECG, the septum, the papillary muscles, and part of the internal ventricu-

lar walls are excited, and at A their contraction begins to elevate pressure in the ventricle. This rise proceeds but slowly from A to B while additional fractions are still entering into the contraction process. The author (1927) therefore designated this as the *entrant phase.* The rise is sufficient, however, to snap the mitral cusps into apposition at B. Therefore, contraction is essentially isometric from B to C, but still not quite so, because the ventricle changes its shape and the valves yield little The latter are responsible for brief oscillations transmitted to the atrial and aortic pressure pulses under favorable conditions Toward the end of this phase, ventricular pressure exceeds the end-diastolic pressure in the aorta. Apparently the rapid rise of intraventricular pressure is transmitted to the aorta as soon as a mere slit appears in the aortic valve causing an initial sharp rise in the aortic pressure pulse. The expulsion of blood quickly follows as the valvular orifices open more fully

Maximum Ejection Phase. Since ventricle and aorta form a common cavity, the pressures increase parallel to a rounded top, pressure in the ventricle exceeds that in the aorta by only a few millimeters of mercury. The ventricular volume curve reveals that about two-thirds of the entire stroke volume is displaced into the aorta during this phase of the cycle (C–D). As already stated, expulsion is achieved chiefly by diminution of the transverse diameters of the ventricular cavity and, to a minor extent, by its decrease in length. This reduction in diameters brings it about that the load on contracting muscle fractions is not increased as aortic pressure rises, indeed, rough calculations by Burch suggest that the load may actually decrease In this respect, the cardiac pump is superior to reciprocating pumps commonly used in industry

Reduced Ejection Phase. During the latter portion of systole (D–F), it is apparent from the ventricular volume curve that the rate of ejection is markedly reduced Several factors probably combine in causing this diminishing rate of discharge despite the fact that the cavities still contain a considerable residual volume. These factors are (1) the natural tendency of a muscle contracting under auxotonic conditions to diminish its rate of shortening; (2) the transfer of the major force of contraction to the more external layers of ventricular muscle, (3) the smaller expulsion of blood per unit of muscular shortening in a diminishing ventricular cavity; and (4) the possible deletion of fractionate contractions toward the end of systole, i.e , approximately at E. Since the aortic uptake is less than the efflux from the aorta, aortic pressure declines and pressure in the ventricle follows (O. Frank).

During the entire period of ejection (C–F) the continuing flow of blood into the left atrium causes its pressure to rise slowly, as shown by the atrial pressure curve.

Ventricular Relaxation and Filling. The dynamics of ventricular relaxation and the part that it plays in ventricular filling are fully as important as the cardiodynamics of ejection With cessation of contraction in all fractions of the myocardium at F, as evidenced by electrographic, myographic, and excitability studies, *the ventricular muscle relaxes very rapidly owing to release of elastic forces created during contraction* There is no evidence that an active muscular process is concerned, the energy of preceding contraction stored by distortion of the ventricular bundles and by development of interfacial tensions is again expended during diastole It is for this reason that the rate at which intraventricular pressure declines from F to H correlates so well with the rate of pressure development from A to C, under different cardiodynamic conditions. It is through such a mechanism, for instance, that the sympathetic nerves and epinephrine not merely increase the force of contraction but store more elastic energy for a more rapid relaxation. A study of pressure-volume plots, to be considered presently, together with other recent studies (Brecher, 1956a), strongly suggests that the elastic forces are not entirely spent during the rapid decline of pressure; owing to a sort of hysteresis, a slow after-extension persists from C to H and perhaps even later With this general picture of the relaxation process, the happenings during successive phases of diastole may be considered

Protodiastole and Isometric Relaxation. With the onset of the elastic recoil at F, pressures decline abruptly in the common ventricular and aortic cavities The slight backflow of blood occasioned in the root of the aorta carries the semilunar leaflets with it until they

approximate at F, thereby causing the second sound The vibration thus occasioned is also recognizable in the atrial pressure pulse. This phase, marked by sharp incision in the aortic pressure pulse (incisura), therefore represents a *protodiastolic phase*. It should be noted that the beginning, not the bottom, of the incisura represents the precise end of systole.

Following closure of the semilunar valves at G, pressures decline in the aorta at a rate corresponding to the drainage of the aortic reservoir. Intraventricular pressure, however, continues to decline sharply for another 0 06 sec before it falls below that of the atrium Since blood neither enters nor leaves the ventricle during this phase of relaxation, it represents the true *isometric relaxation phase*

Rapid Inflow Phase. As soon as left ventricular pressure drops below that of the left atrium at G, the mitral valve opens and a large fraction of the left atrial blood rapidly drains into the left ventricular cavity (G–H), as shown by the volume curve and a simultaneous drop in [illegible]

[illegible] Since this enlarges the left ventricular *cavity, the chordae tendineae* become taut, and the mitral leaflets are again drawn together to form a narrow aperture (Rushmer et al) It has become customary to assign this filling almost entirely to the pressure in the left atrium at the moment that the mitral valves start *to open However, it has* long been suspected *and more recently demon*strated (Brecher, 1956a) that *the pressure dif*ference during this phase *is* partly determined by continued release of elastic forces However, it is inadvisable, *in the author's opinion*, to designate such a process as "suction," as several recent authors *seem* inclined *to do*

Diastasis. When the heart rate *is not* too rapid, filling of the ventricles continues at a slow rate (I–J), termed *diastasis* The elastic recoil forces *are* at a minimum, the mitral valve has partly closed, and atrial pressure has declined Hence, the inflow is greatly retarded, but a considerable volume may still be added to the ventricles if atrial filling is good during this period

Atrial Systole. Ventricular volume curves indicate that five-sixths of the diastolic filling has been attained at the end of diastasis (J). Atrial contraction (J–K) not only adds to the other fractions but also slightly elevates left ventricular pressure As pressure and volume curves alike indicate that some recession takes place during the latter half of atrial contraction, it is likely that some reverse flow occurs. This could carry the AV valves back toward a position of closure, preparatory to the complete closure at B on the pressure curve. The question as to whether such closure is accompanied by slight regurgitation has been debated beyond its merits Some displacement of liquid must occur if the valves close by a hinge movement as appears to be the case, and the answer depends on whether one regards the fraction of blood on the atrial side of the open mitral valve as being in the ventricular or atrial cavities

Time Relation to Successive Phases. The durations of the successive *phases of the heart* cycle in dogs at a *heart rate of* 75 per minute are *shown in Fig* 2-28 *and are* essentially the same as in man. These average as follows. isometric contraction, 0 05 sec, maximum ejection, 0 09 sec, reduced ejection, 0.13 sec, *proto*diastole, 0 04 sec, isometric relaxation, 0 08 sec, rapid inflow, 0 11 sec, diastasis, 0 19 sec, atrial systole, 0 11 sec.

MOVEMENT OF BLOOD IN THE AORTA

At the onset of ventricular ejection, the aorta is already distended with blood What happens to the substantial increment added during each systole? Approximately 60 to 65 per cent of the systolic uptake is accommodated by pushing the existing blood out of the thoracic aorta and its branches; the rest is stored in the aorta by stretching its walls and is moved forward during the succeeding diastole.

The average rate of flow is approximately 18 cm/sec *in* the aorta and about 14 *cm/sec* in branches *such* as the brachial and femoral arteries However, this gives a very incomplete picture Actually, the velocity of flow accelerates brusquely shortly after ejection to a peak velocity of 100 cm/sec slightly before the maximum systolic *pressure is reached* It then decelerates to 20 *cm/sec at the end of* systole and to 20 cm/sec or less during the succeeding diastole In some arteries, such as the axillary, femoral, common carotid, and coronary vessels, a transient backflow reaching a negative velo-

city of 30 cm/sec takes place at the onset of diastole (McDonald).

RELATION OF PRESSURE PULSES TO OTHER CARDIAC EVENTS

Relation to Right Ventricular Events. The onset of the pressure rise in the right ventricle bears a variable relation to that of the left ventricle in dogs; either may precede. However, isometric contraction is shorter, ejection starts earlier and lasts a little longer than on the left side. These differences are probably explained by the lower pressures in the pulmonary circuit. During isometric relaxation, the pressure falls more gradually, hence this phase is also a bit longer Similar relations have been described in man, but the precedence of right ventricular systole is said to be the more consistent one.

Relation of Contractile and Electrical Events. Comparison of local contraction and electrical variations indicates that contraction starts at *the peak of local differential electrograms* (Eyster and Meek, 1914) Similarly, the transmembrane potential of papillary muscle precedes isometric contraction by 0 01 sec, but repolarization may be complete before onset of relaxation (Brooks et al, 1955)

Since ventricular contraction begins with a recruitment and ends by demobilization of contractile elements and since electrocardiograms recorded from the body surface likewise represent resultants of vectors, it is rather remarkable that close relations between mechanical and electrical systole do exist In brief, the elevations of the P and R deflections in lead II precede contractions of the atria and ventricles, respectively. More specifically, right atrial systole commences at the summit of P, and left atrial systole does not start until after the completion (Fig. 2-28, J) Left ventricular systole starts at or slightly beyond the peak of R The T deflection is commonly, though not always, completed before the end of mechanical systole of the left ventricle

The relation of the pressure pulses to the heart sounds is indicated in Fig 2-28 but will be discussed elsewhere.

Relation of Pressure Pulses to Excitability. The left ventricle is absolutely refractory to electric stimuli of intensities that can be generated in the body during the early period of systole (approximately A–E, Fig 2-28), it is relatively refractory during the latter part of systole and isometric relaxation (approximately E–H). Excitation during these periods evokes mechanical responses after the completion of isometric relaxation; hence the latency of response apparently increases as stimuli are applied earlier and earlier. It has been found, however, that strong, brief electric shocks applied at any time during reduced ejection may not only elicit a premature contraction but also induce ventricular fibrillation. This, however, appears to be due to persistence of artificial polarization by the electric shock and, therefore, does not contradict the law of refractoriness (Moe et al.).

Determinants of Cessation of Contraction. It is well established that the duration of left ventricular contraction is almost a linear function of the duration of the preceding diastole, i.e, it decreases with cardiac acceleration Furthermore, at constant heart rate, this duration is affected by changes in diastolic size, *aortic resistance, blood electrolytes, adrenergic* influences, and drugs. However, knowledge as to how and why such changes in the duration of contraction are brought about is still meager. The change does not involve onset of contraction or difference in the rate of recruitment (Wiggers). Most probably it involves intrinsic changes in the ultimate mechanism of contraction Holt (1957) has presented evidence that shortening of ventricular muscle stops when it meets a force that it cannot overcome.

MATHEMATIC ASPECTS OF CARDIAC CONTRACTION

Attempts to express mechanical processes of contraction in mathematic terms require reduction of factors to their simplest terms and frequent assumption of conditions that do not exist For example, it has been calculated that reduction of an atrial cavity by one-half during its contraction should increase intraatrial pressure eightfold However, the required assumption that the force of contraction remains constant until the end of contraction does not obtain

Nevertheless, mathematic and physical considerations have furnished valuable general principles that must not be overlooked in the evaluation of pressure pulses For instance, it has long been recognized that reduction in the size of the ventricular cavity during ejection

involves more shortening of internal than of external muscle fibers, a reduction in the internal surface area, greater wall thickness, and exposure of more fibers per unit area to luminal pressure These facts allow a number of important generalizations. (1) since the radial force that must be overcome by contraction is a product of pressure and surface area, the total force that must be overcome decreases as contraction proceeds, (2) since the internal surface decreases more than the external surface, the more external muscles must assume larger and larger shares of the contractile burden as ejection proceeds (Burch, Rushmer, 1956). If, on the other hand, the diastolic volume increases, a proportionately greater force is necessary to elevate luminal pressure by a definite amount. For instance, it has been estimated that a twofold increase in diameter requires eight times as much force to cause an equivalent elevation of cavity pressure Fortunately this physical disadvantage of ventricular distention may be more than compensated by a better physiologic response of contractile units

Ventricular Work. Each ventricle performs work in ejecting a definite volume of blood against pressure, in imparting movement to it, and, in addition, in producing deformation and stresses in the heart itself A complete expression of the work of the heart is given by the mathematic equation of O Frank.

$$w = \underset{(1)}{\int_{V_1}^{V_2} P\,dV_2} - \underset{(2)}{\int_{V_1}^{V_4} (D)\,dV} + \underset{(3)}{\sum \frac{dmv_1^2}{2}} - \underset{(4)}{\sum \frac{dmv_2^2}{2}} + \underset{(5)}{R} + \underset{(6)}{At}$$

Term 1 expresses the potential or pressure energy imparted to the arterial system.

Term 2 denotes the potential energy developed by elastic physical forces in the ventricular wall and must naturally be subtracted

Terms 3 and 4 represent the kinetic energy (K E) developed in the aorta minus any remnant of K E left over as a result of inflow.

Term 5 represents the elastic strains developed within the ventricular wall.

Term 6 comprises the potential and kinetic energies required for producing movements of moieties of ventricular myocardium without degradation into the heat.

At present there is no means of estimating all the energies required for calculating work in accordance with formulas of this kind, and workers commonly resort to use of the formula

$$W = QR\frac{mv^2}{2}$$

where Q = stroke volume

R = the mean arterial pressure in meters of water

m = the mass of ejected blood

v = velocity

Since the kinetic factor is not easily determinable, it is generally disregarded. However, it should be recognized that it may increase considerably when the stroke work becomes large. Since blood is expelled against the aortic pressure which exists during systole (not that which obtains throughout the whole heart cycle), it is more accurate to use systolic mean pressure, obtained by integration of the aortic pressure pulse, for R in the above equation

The Work Diagram. An area diagram of ventricular work can be constructed by plotting pressure changes on the ordinate and corresponding volume changes on the abscissa If this is done using the pressure curve of the left ventricle and the combined ventricular volume curve of Fig 2-28, a plot such as shown in Fig 2-29 is obtained. The lettering of the two figures correspond. In reading the tracing counterclockwise, it is seen that during isometric contraction (A–C), intraventricular pressure rises without change in volume. During maximum ejection (C–D), aortic uptake increases greatly as pressure rises, but during reduced ejection (D–F), a smaller uptake occurs with declining pressure. During isometric relaxation (F–H), there is only a small increase in ventricular volume—probably because of filling of the coronary vessels—with a maximum drop in pressure The fact that the curve is convex to the abscissa during the phase of rapid inflow (H–I), that is, that the pressure continues to decline with rapid increase in ventricular volume, suggests that the force of elastic recoil aids inflow during this phase. However, the rise of the tracing from I to J, suggests that the filling during diastasis is controlled by atrial pressure

While such plots are highly instructive in a general way, they are inexact owing to the necessity of using volume curves of the two

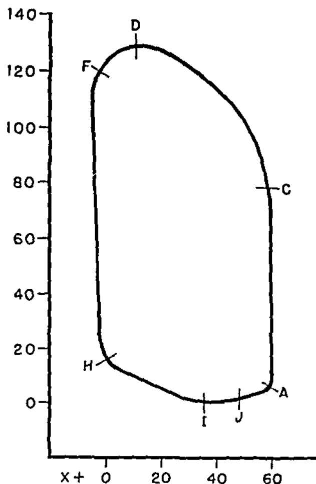


Fig 2-29. Work diagram of heart constructed from left ventricular pressure and volume curves shown in Fig 2-28 Lettering corresponds to curves of Fig. 2-28.

ventricles Katz and Katz, however, constructed a few work curves from an animal preparation in which the left volume curve alone could be recorded. They found that when a hypodynamic left ventricle was stimulated by norepinephrine, the work plots shifted decidedly to the left, suggesting that the inherent viscoelastic properties were altered Calculations indicated also that the contribution of K E to the total work was doubled

The Economy-of-effort Index. If the ventricle contracted isometrically, i e, without change in volume, the area under the ventricular pressure curve (tension-time) would serve as an index of the mechanical energy liberated However, the heart *in the body beats in an after-loaded* fashion and, in so doing, probably liberates more mechanical energy. In 1928 the author and Katz proposed a comparison of the static and dynamic energies developed during the phases of ejection as an *index of the economy* with which the ventricle expels blood under different circumstances The idea may be expressed by the following analogy: in order to throw the content of a pail with some force over a high wall *it is necessary to raise* the pail and sustain it above the wall level for some time This represents static and expendable energy. In addition, energy is required to empty a pail over the wall. This is dynamic energy.

In applying the principle to left ventricular pressure curves, they were divided, as shown in Fig. 2-30, so that the static pressure developed during ejection (area *B*) and the dynamic pressure used in overcoming resistance and in propulsion of blood during the succeeding diastole (area *A*) could be expressed as a ratio, *B/A*. Such comparison seemed allowable since *the changes in ventricular volume* during successive moments of ejection affected both areas equally. While the ratio *B/A* is not an expression of the mechanical efficiency of the left ventricle (work energy/total energy), various studies indicate that it *alters directionally if not quantitatively* with mechanical efficiency under varying dynamic conditions.

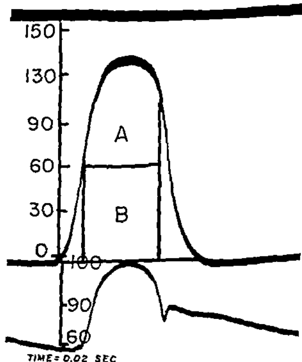


Fig. 2-30. Demarcation of areas indicating dynamic effort, A, and static effort, B, of left ventricle during ejection. Upper-left, ventricular pulse; lower, aortic pressure pulse Time, 0 02 sec.

9

Cardiac output, stroke volume, and stroke work

CARL J. WIGGERS

The term *cardiac output* has come to mean the volume of blood ejected by the left ventricle into the aorta per minute *Stroke volume*, also called systolic discharge and pulse volume, denotes the volume ejected per beat In common parlance *stroke work* signifies the product of stroke volume and mean arterial pressure, it is an approximation only

CARDIAC OUTPUT IN INTACT ANIMALS AND MAN

Methods. Quantitative estimates of cardiac output of intact organisms during states of health and disease have been attempted through use of various technical principles [1] The most commonly used procedures and, with proper precautions the most satisfactory, are applications of the Fick gasometric and the Stewart dilution principles

Fick (1870) suggested that if the oxygen consumption and the per cent difference in oxygen content of arterial and mixed venous blood are known, it is an easy matter to calculate the volume of blood per minute required to carry the added oxygen, i e, the cardiac output The principle, first applied experimentally to horses by Zuntz and Hagemann (1898), became adaptable for routine human use with the development of right heart catheterization (Forssman, 1929, Cournand and Ranges, 1941)

Stewart (1897) proposed and utilized a blood-dilution method, which has undergone repeated improvements An innocuous solution that can be easily detected in peripheral arterial blood is quickly injected into a vein or directly into a cardiac chamber Knowing the amount injected and its mean concentration in a peripheral artery over a short interval, the volume of blood required for its dilution, i e, the cardiac discharge for that interval, can be calculated Thus, if 12 mg of a dye is quickly injected and an average concentration of 4 mg is found in arterial blood during the succeeding 30 sec, the dye must have been diluted by 3 liters of blood, giving a cardiac output of 6 liters

In addition to these two procedures, a number of empirical methods have been developed which involve the use of constants derived from comparisons with the foregoing gasometric or blood-dilution techniques. These include the use of the ballistocardiogram, electrokymogram, roentgenkymogram, dielectric procedures, and computations based on pulse pressure or analyses of previous pulses (for descriptions, critique, etc, of various methods, see Wiggers, Hamilton, and Luisada).

Normal Values and Variations. The cardiac output of healthy adults in basal states ranges approximately between 3 and 6 5 liters Since differences in body height, weight, and form account largely for the variation, it has become customary, following a suggestion of Grollman, to compute values on a basis of square meter surface area, the so-called *cardiac index* This

[1] See Part 4, Chap 13 *Editor.*

approximates 3 liters; however, it is desirable in following effects of various stresses, to determine the basal cardiac index for any given individual more exactly.

Studies by different groups indicate that the basal cardiac index is not affected materially by age, sleep, active change of posture, or reasonable variations in environmental temperature. The index tends to be slightly lower in females, does not change much during menstrual periods, but is, of course, increased significantly during pregnancy The cardiac index increases up to 30 or 40 per cent after consumption of food, intake of large volumes of liquids, during muscular exercise, and as a result of emotional reactions. It is higher following use of cardiac stimulants, such as digitalis preparations, epinephrine and allied compounds, atropine, etc Moderate smoking does not appear to increase the cardiac index; excessive smoking does.

Some Pathologic Changes. The basal cardiac index is increased during fevers and hypoxic states, including anemia, also in hyperthyroidism and in the presence of AV fistulas. It is reduced to varying extent by such disturbances as marked cardiac irregularities or tachycardias, coronary thrombosis, shock, hypothyroidism, pneumothorax, and pressure breathing It is often, but not necessarily, reduced as a result of left heart valvular lesions Clinical investigators recognize "high-output" and "low-output" types of congestive heart failure

THE REGULATION OF CARDIAC OUTPUT

The Objectives of Animal Experimentation. Studies on intact organisms by methods outlined above have offered suggestive evidence as to the manner in which cardiac output is controlled, but the most definitive analysis of basic mechanisms has accrued from experimental studies on animals. These studies have given rise to principles or laws according to which ventricular muscle performs its function of expelling blood For such studies, special preparations of the circulation and special forms of flowmeters have been designed The criticisms that such circulations and methods of study are artificial and indicate what the heart "can do rather than what it does" are of course valid, but in no sense derogatory On the contrary, ingenuity in devising new experimental approaches to test the regulation of cardiac performance under different conditions should perhaps be regarded as a mark of experimental eminence.

The methodologies used and the data acquired by such experimental analysis will, therefore, be analyzed first, and an attempt to synthesize facts into the working of the heart in the intact organism will be deferred to the latter part of this chapter

Experimental Methods. For most animal studies, *flowmeters* of varying design and accuracy have been inserted into the aorta, the venae cavae, or the pulmonary artery of exposed hearts. The latter obviously offers the only place in the circuit where the whole stroke or minute volume of the ventricles can be measured The flowmeters used range from the earlier models of *Stromuhren* of Ludwig, Tigerstedt, and Hurthle to more modern devices, such as rotometers, thermoflowmeters, orifice meters, turbonometers, electromagnetic and bristle flowmeters, etc. (O. Frank, Gregg and Brecher).

The use of ventricular volume curves, introduced by Henderson (1906), remains, in the author's opinion, one of the most useful methods for analyzing the responses of the ventricles to mechanical, humoral, and nervous influences. This takes into account criticisms of the procedure on theoretical grounds or by those who have never acquired the technique for their proper use It is true that cardiometric recordings have their limitations, but so have all procedures so far devised, they are susceptible to errors, but these can be taken into account or avoided Of prime importance is the check of records taken at high speed synchronously with pressure pulses from the aorta (Wiggers and Werle) Advantages of studying the heart that remains connected to a natural circulation over heart-lung and similar preparations are many since the body circulation can be kept intact, one avoids cannulation of large vessels, temporary impairment of cardiac circulation, use of artificial tubings and resistances, use of anticoagulants, all of which appear to be concerned in causing progressive cardiac failure By various expedients (use of a controlled circulation preparation) heart rate, venous return, and aortic resistance can be altered independently, as in artificial circuits (Wiggers, 1952) Stroke volumes can be re-

corded beat by beat; they need not be averaged. Changes in diastolic and systolic size can be evaluated, and the detailed alterations in filling and ejection can be recorded more accurately than by any other known procedure. By recording various combinations of right and left atrial, pulmonary arterial, and aortic pressure pulses simultaneously with volume curves, it is generally possible to determine whether alterations depicted in volume curves represent changes in the right or left ventricle or in both. However, recent experimental evidence suggests that in the past too little attention was paid to such differentiations and to independent changes in systolic size or residual volume.

PRIMARY AND SECONDARY DETERMINANTS OF CARDIAC RESPONSE

Changes in responses of cardiac muscle are *determined* by their primary state of contractility and by *secondary influences* that play upon it.

The magnitude and force with which moieties or masses of *ventricular muscle* respond to excitation depend basically on the "condition" or "reactive capacity" of the muscle. This may mean its power to release total energy, its ability to transform a larger or smaller fraction of total energy to mechanical forms, or both. This attribute of variable *response is not at* variance with the "all-or-none" characteristic of cardiac muscle, which *means the fullest response* which a muscle can give at any existing state of contractility.[2]

The reactive capacity of cardiac muscle is determined by diverse environmental influences such as temperature, the balance of sodium, potassium, and calcium ions, pH, hormones, nerves, drugs, etc. It may vary from beat to beat, as illustrated by the classical "treppe" or "staircase" which follows repeated excitation, and also by the development of fatigue from overfrequent excitation.

The response of large masses of cardiac muscle may also be impaired through deletion of cardiac fractions as a result of their failure to be excited (blocks) or through their injury (e.g., inadequate blood supply). Finally, reduction in response may follow a slower, aberrant spread of excitations, as in ventricular rhythms.

In view of the many ways in which the inherent responsive state or "condition" of heart muscle can be quickly altered, it is important in assessing secondary factors (such as changes of heart rate, filling, and resistance to ejection) that the innate condition of *heart muscle* be kept as constant as possible. Hearts studied in animals with opened chest and under artificial respiration operate under unsteady states of basic reactivity unless expedients are used to stabilize the influence of anesthetics, to compensate for effects of operative procedures, and to maintain the gases and acid-base balance of the blood at constant and normal levels. It is equally clear that use of blood rendered incoagulable, often diluted with saline solution, ventilated artificially, and passed repeatedly through artificial tubings and unnatural resistance quickly leads to impaired contractility in artificial circuits. The conditions under which experiments are performed must, therefore, be taken into consideration in evaluating patterns of response.

Regulation of Cardiac Output by Heart Rate. Henderson (1906), on the basis of recorded volume curves from the ventricles, concluded (1) that the ventricles fill and empty according to a fixed geometric pattern as long as venous supply does not fall below *normal* levels, and (2) that further *increase in* venous supply cannot augment ventricular filling and stroke volume. In short, according to the *law of uniformity of behavior*, cardiac output increases progressively up to rates of 180 per minute, thereafter becomes stationary, and *diminishes* again during extreme tachycardia.

Diametrically opposed to this conclusion was the report by Starling and his coworkers that when arterial resistance and venous inflow are kept *constant* (within limits of their heart-lung

[2] "The weakest induction shock which will just cause a contraction of the heart, does not evoke a minimal contraction, and the size of the con-... produces the greatest contraction that can be produced by any strength of stimulus in the condition of the muscle at the time. From this, it follows directly that the cause of the varying degrees of contraction of the heart is to be sought in changing (actual) conditions of the muscle fibres themselves. It is scarcely necessary to point out the great practical significance of this generalization." (Translation of the all-or-none law—Bowditch.)

preparation), cardiac output is affected very little by changes in heart rate between 60 and 160 per minute.

Effect of End-diastolic Volume and Pressure. O. Frank (1895) concluded that stepwise increases in end-diastolic volume cause corresponding increases in end-diastolic ventricular volumes and pressures in the isometrically and isotonically contracting frog heart. In other words, the initial tension under which the contraction started appeared to determine the magnitude of the all-or-none response.

The author (1914) found that the reaction of the right ventricle of dogs operating normally in an afterloaded manner also obeys the same rule. Progressive increases in venous return were accompanied by simultaneous augmentation of the ventricular end-diastolic pressure, the isometric contraction gradient, the peak pressure, and the duration of systole. Similar conclusions were reached by H Straub in the case of the left ventricle. However, Starling and his group, working with their newly developed heart-lung preparation, found that the end-diastolic volume could vary considerably without a change in end-diastolic pressure Hence, they concluded that *the initial length of muscle fibers, rather than tension, determines ventricular response.* These observations, supported by cognate studies on isometrically contracting hearts of turtles, led to the generalization commonly called *Starling's law of the heart.*

Starling (1918) reproduced a curve which is actually a duplicate of one previously published by O Frank (1895), except that probable ordinate and abscissal values for a contracting dog's heart were added The curve reveals that progressive increase in stretch of ventricular muscle up to an optimum filling releases more and more tension energy *in an isometrically contracting ventricle* but that further stretch results in a rapid diminution of contractile tension despite a rapid increase in initial tension. It would, therefore, seem more appropriate to designate these relations as the *Frank-Starling law.* Subsequent investigators have taken the liberty of substituting cardiac output of the naturally beating heart for the contractile tension, but Sarnoff et al (1954) have utilized stroke work as a nearer approach to energy release of the heart contracting in an afterloaded manner

Such "ventricular function curves," determined separately for the right and left ventricles, failed to show the diminishing limb even when left atrial pressure exceeded 300 mm saline in "normal" hearts; but it did occur when myocardial depression supervened or when the pericardium was removed (Berglund et al.).

EFFECT OF VARIOUS DETERMINANTS ON VOLUME CURVES

Dominant Effect of Heart Rate. The most significant and most generally confirmed contribution of Henderson to the mechanism of cardiac filling and ejection was the observation that the diastolic size of the heart, as commonly determined by roentgenography, is fundamentally determined by the heart rate However, as insight became clarified by other types of investigation, a reexamination of ventricular volume curves yielded new information as to the mechanisms by which such changes in diastolic size are achieved, through influences of the vagus and sympathetic nerves.

Effect of Vagal Slowing. The greatly reduced black insert of Fig 2-31 shows a "slow paper" recording of ventricular volume changes

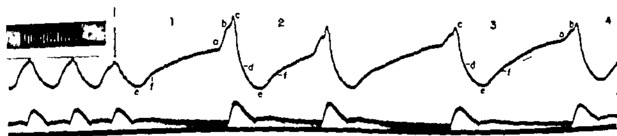


Fig. 2-31. Optically recorded volume curves of two ventricles (down stroke = systole) with aortic pressure pulse (below) showing effects of vagus stimulation. a–b, Atrial systole; b–c, isometric contraction; c–d, maximum ejection, d–e, reduced ejection, e–f, rapid inflow, f–a, diastasis. Black insert, slow-drum tracing of similar vagus effect. Discussion in text.

during cardiac deceleration from a rate of 120 to 64 per minute during vagus stimulation (Reading the record from right to left illustrates equally well the effect of sudden sinus acceleration) The brief deceleration was accompanied by an uncompensated decline of mean arterial pressure from 118 to 82 mm Hg. The immediate effect of slowing consisted in an immediate increase of diastolic volume which soon stabilized. In general accord with the Frank-Starling law, the stroke volume of both ventricles increased, but, contrary to reports of Starling and his group, the minute output did not remain constant; it decreased from 760 to 504 ml/min In general, the immediate effects of heart rate on minute output more nearly follow the predictions of Henderson The main records of Fig 2-31 show a few vagal beats following a series of control beats at a rate of 140 per minute, as recorded optically on rapidly moving paper They show the variable ways in which a large diastolic size can be accomplished in successive beats The rate and magnitude of rapid filling (*c–f*) during continuing relaxation of the ventricles is not altered In the first two vagal beats, the greater diastolic filling is not accomplished merely by continuing filling during the prolonged diastasis (*f–a*) but by an increased input during atrial contraction (*a–b*) as well This apparently represents a response of the atria to a greater diastolic stretch However, this effect is soon overpowered by the negative inotropic effect of the vagus on the reactive capacity of the atria, with the result that the atrial input is reduced in the third and fourth beats. Here diastolic size is determined by a more rapid and prolonged filling during diastasis In response to the greater diastolic size—and fully in accord with the Frank-Starling concept—a larger systolic discharge is accomplished by a more rapid and extensive emptying during the maximum ejection phase (*c–d*) and a prolongation of the reduced ejection phase (*d–e*).

Responses to Sympathetic and Sympatheticovagal Actions. Since the cardiac sympathetic nerves augment ventricular contractions as well as increase heart rate, the contour of ventricular volume curves is further modified And when parasympathetic and sympathetic influences are operating at the same time, as probably happens frequently in everyday life, the effects on ventricular filling and emptying become more complex.

Their operation can be analyzed conveniently by recording the volume changes that take place immediately after injection of a small dose of epinephrine and again after a slowing has been induced through pressoreceptor reflexes. Segments *A* and *B* of Fig 2-32 show the primary adrenergic effects, viz, cardiac acceleration and considerable increase in stroke volume with larger systolic and diastolic sizes of the ventricles. Despite the more rapid filling during early diastole, a larger atrial input, and a more rapid rate of expulsion, the ventricles are unable to empty as completely as in normal conditions because of the higher arterial resistance. As soon as reflex slowing supervenes, the situation changes, as shown in segment *C*. The adrenergic stimulating effects on ejection velocity and on atrial input are retained, but, owing to the prolongation of diastolic filling with greater diastolic size, the stroke volume increases so much that the systolic size of the ventricles becomes less than in segment *A* of the control curve

Such studies reveal the complicated series of factors that can affect filling and emptying when the heart rate is modified They emphasize the importance of controlling heart rate in studying the effect of mechanical determinants on cardiac output This was achieved by clamping the SA node and driving the heart electrically at constant rates through electrodes attached to the right atrium

Responses to Increasing Venous Return. Howell and Donaldson were apparently the first to demonstrate that at constant heart rate, the cardiac output of an isolated heart preparation *is increased* by a larger input of blood Starling and his group demonstrated the relationship in a more quantitative fashion The author and Katz (1922) analyzed the manner in which stroke volumes were augmented in an open-chest preparation in which heart rate and aortic diastolic pressure were kept constant In these experiments, the rate of venous return was increased progressively, not abruptly as in experiments by Starling's groups As shown in Fig 2-33A, the initial increases in stroke volumes are accomplished not merely by expelling the additional volume which accumulates in the ventricles during diastole, but also by ejecting *some of* the residual systolic vol-

time. As the rate of venous return continues to mount, stroke volumes still continue to augment with increasing diastolic size but the systolic residual volume becomes larger again. The configuration of volume curves recorded on rapidly moving paper and shown at *A* and *B* to the right of Fig. 2-33A reveals that the ejection of larger stroke volumes is accomplished largely by greater velocity of ejection and to a lesser extent by prolongation of systole There appears no question, therefore, that at constant heart rates the ventricles increase their stroke volumes in accordance with the Frank-Starling law up to the time that pressure in the right atrium has risen to even higher levels. However, when the rate of venous return increases above a critical value, the rate of diastolic distention starts to increase rapidly because the stroke volumes diminish progressively. As shown by curve *C* to the right, the rates of ventricular filling and discharge are then both very slow. On such a basis, it may be concluded that, in accordance with the Frank-Starling law, the two ventricles, acting as a unit, are able to compensate for increasing rates of diastolic filling up to a critical level, beyond this they fail, causing a rapid rise of atrial and venous pressure because the returning blood can no longer be expelled at an equivalent rate.

Since Sarnoff et al (1954) have produced

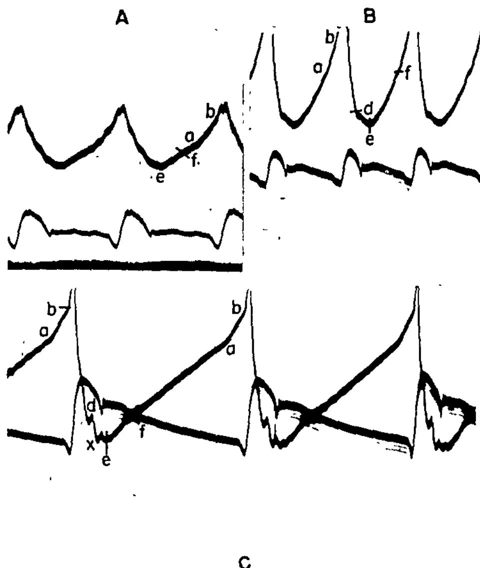


Fig. 2-32. Three segments of optically recorded ventricular volume curves (upper) and aortic pressure pulses (lower). A, Control [venous pressure (v p), 102 mm H_2O], B, effect of epinephrine (v p., 120 mm H_2O), C, same later, after vagal slowing (v p, 144 mm H_2O); X, artifact. Lettering as in Fig. 2-31.

evidence that the stroke work of the normal left ventricle does not diminish even when left atrial pressure reaches 410 mm saline, it must be granted that the inherent capacity of ventricular response may have been impaired as a result of the large volumes of saline infusion required to produce these effects In addition, a reexamination of simultaneously recorded volume and aortic pressure curves has revealed that the latter were often not altered as to magnitude or form for some time after the stroke volumes of both ventricles had displayed a marked reduction. This strongly suggests that the initial reductions in stroke volume and augmentation of diastolic size after *B*, Fig 2-33A, may be due to failure of the right ventricle This interpretation is supported by a review of cinematographic films taken under similar conditions Apparently the left ventricle is able, to judge from aortic pressure pulses, to maintain large stroke volumes as long as a surplus volume remains in the left atrium and pulmonary bed After this, the stroke volumes of the left ventricle also decline, *not because it is unable to respond to increasing diastolic stretch, but because the right ventricle is unable to deliver adequate volumes of blood.* In short, the heart as a whole is able to compensate for increasing volumes of venous return as long as the right ventricle can augment its stroke volume in accordance with the Frank-Starling law.

Reactions to Increased Aortic Resistance. In the intact circulation, an abrupt elevation of aortic pressure, as for example by sudden compression of the aorta just above the diaphragm, causes the changes, though less severe, described by Starling et al in the heart-lung preparation The stroke volumes of the two ventricles are decreased immediately by less complete emptying Since right ventricular and

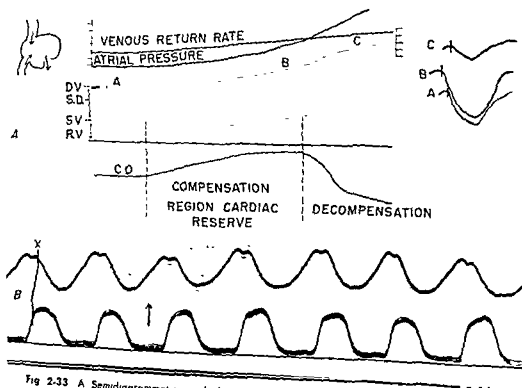


Fig 2-33 A Semidiagrammat... infusion of 750 ml saline soluti... systolic volume, S V., systolic c... ...ual volume, R V Copies of volume curves recorded on rapidly moving paper on right at corresponding points, *A, B, C* B Volume curves of ventricles (upper) and left ventricle pressure curves (lower) showing effects of partial aortic compressors at arrow Note elevation of end-diastolic pressure in left ventricle with increase in diastolic volume in third and fourth beats after arrow *X*, Correction for delay in transmission of volume change in this experiment

pulmonary pressure pulses reveal no changes, the greater systolic and diastolic volumes of the two ventricles are essentially produced by effects on the left ventricle. However, the greater residual blood added to normal diastolic inflow soon stretches the fibers of the left ventricle so that, in accordance with the Frank-Starling law, stroke volumes are restored to normal, or occasionally even exceed it (Fig. 2-33B). At this stage, left ventricular pressure pulses display a small, but measurable, increase in end-diastolic pressure, a greater force of contraction (steeper pressure rise during isometric contraction), and a higher pressure summit The duration of systole is primarily decreased in reaction to the higher aortic resistance but gradually increases as diastolic distention develops.

Since such an abrupt increase in aortic pressure is less apt to occur during life, the effects of a more gradual increase in total peripheral resistance deserve analysis. This has been ac-

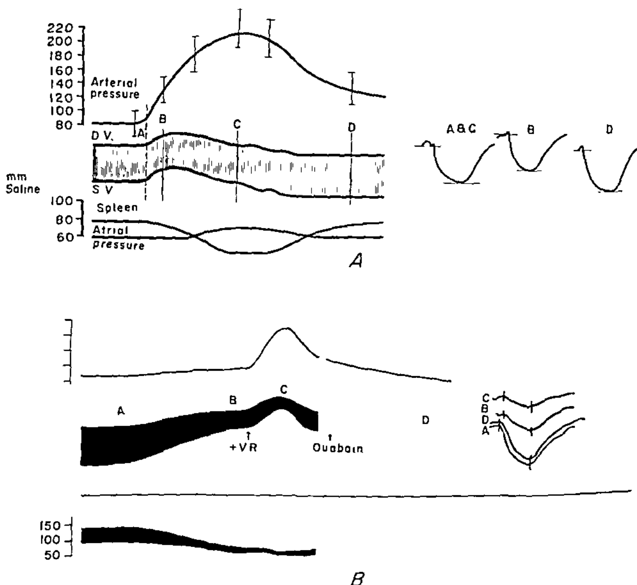


Fig. 2-34. A. Copy of slow-drum record showing effect of progressive increase in mean pressure and pulse pressure following reflex vasoconstriction on diastolic, *D V*, and systolic volume, *S V*. Curves to right, copies of records on rapidly moving paper. *B* Semidiagrammatic graph of changes actually inscribed on long record showing (*A–B*) successive effects of myocardial depression by chloral hydrate; *B–C*, rapid infusion of 150 ml saline solution Intravenous dose of ouabain as indicated. Upper curve, mean atrial pressure; middle curve, diastolic and systolic changes of ventricle; lower curve, arterial systolic and diastolic pressures Curves to right, tracings of volume curves recorded on rapidly moving paper at A, B, C, and D.

complished experimentally by stimulating the central ends of both divided vagus nerves The reactions, shown in Fig 2-34A, as a retrace of a slow-drum recording, show several features of additional interest. The left ventricle is apparently extremely sensitive to minor elevations of arterial pressure, systolic and diastolic volumes begin to increase when mean arterial pressure has risen only 10 mm Hg (*A*), and both attain their maximum with a rise of only 42 mm Hg (*B*). By the time mean pressure has reached its summit (*C*), systolic, diastolic, and stroke volumes have returned to control levels Therefore, while compensation against higher resistance may be attributed to greater diastolic distention of the left ventricle shortly after *B*, it cannot account for the restoration of equilibrium at *C* The Frank-Starling concept also fails to explain the augmented *stroke* volumes which are accompanied by decreasing diastolic size from C to *D* in Fig 2-34A Nor does the thesis of Holt, that ejection ceases when the force of contraction equals the *counterforce* of resistance, explain such results *The most* probable inference is that the temporary hypertension in some way improves the inherent capacity of ventricular response, enabling the ventricles to eject larger stroke volumes at a lesser degree of diastolic stretch

Effects of Cardiac Depressants and Stimulants. Figure 2-34B, a retrace of a slow-drum record, illustrates the *effects of myocardial depression* induced by chloral hydrate while the heart was driven by *artificial* stimuli to the right atrium The immediate effect consists in a marked reduction in stroke *volume This is* responsible for a greater enhancement of the systolic than of the diastolic volume Corresponding volume curves shown to the right (*A–B*) indicate marked reduction in rates of ejection and filling, the latter because impedance to inflow is greatly increased From *B* to *C*, a rapid infusion of saline was given. The sharp rise of right atrial pressure is accompanied by a similar increase in diastolic size of the ventricles, but the depressed myocardium responds by increasingly smaller stroke volumes. Left ventricular pressure pulses, under such conditions, show a pronounced increase in end-diastolic pressure, a slower isometric gradient, and a lower summit. There appears to be no question but that such depressed ventricles display a descending limb on the Frank-Starling curve.

During the gap shown in the illustration, *ouabain* was administered intravenously and, when an improvement in cardiac output became noticeable, registration was resumed The progressive recovery to a practically normal circulatory state, *D*, scarcely needs description. It is the author's interpretation that digitalis and strophanthus alkaloids *rescue a failing* heart by improving the vigor of contraction and that the progressive reduction in diastolic volume size and venous pressure are secondary consequences.

Effects of Hypoxia. Since it is generally believed that hypoxia and asphyxia exert a harmful influence on myocardial reactivity, it may be stressed that the contrary can be demonstrated by means of volume curves As shown in Fig 2-35, discontinuance of artificial respiration at the time marked by the arrow leads to *progressive dilatation* and increase in stroke volumes Pulmonary and aortic pressure pulses also increase in amplitude, mean pressures rise in both circuits Even when an animal is asphyxiated to the point at which the ventricles

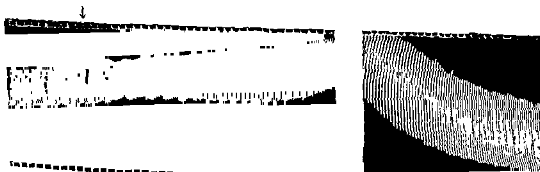


Fig 2-35. Slow-drum record showing effects of asphyxia (arrow) on ventricular volume changes . . . half, recovery after restoration of artificial respiration.

pulmonary pressure pulses reveal no changes, the greater systolic and diastolic volumes of the two ventricles are essentially produced by effects on the left ventricle However, the greater residual blood added to normal diastolic inflow soon stretches the fibers of the left ventricle so that, in accordance with the Frank-Starling law, stroke volumes are restored to normal, or occasionally even exceed it (Fig. 2-33B). At this stage, left ventricular pressure pulses display a small, but measurable, increase in end-diastolic pressure, a greater force of contraction (steeper pressure rise during isometric contraction), and a higher pressure summit. The duration of systole is primarily decreased in reaction to the higher aortic resistance but gradually increases as diastolic distention develops.

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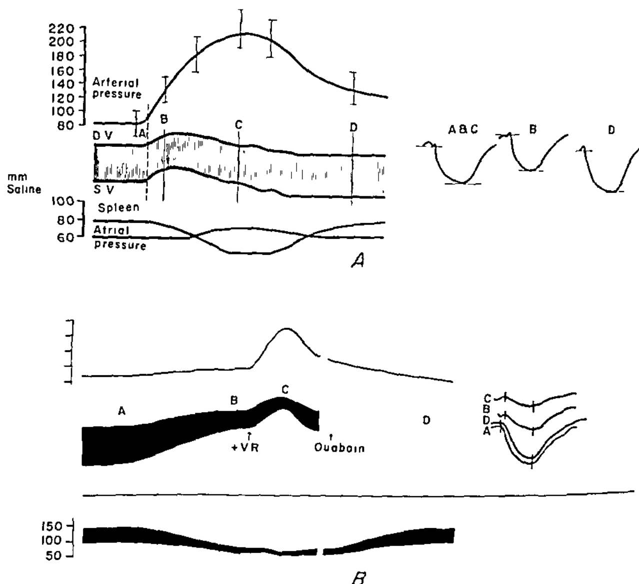


Fig. 2-34. A. Copy of slow-drum record showing effect of progressive increase in mean pressure and pulse pressure following reflex vasoconstriction on diastolic, D V., and systolic volume, S.V. Curves to right, copies of records on rapidly moving paper B Semidiagrammatic graph of changes actually inscribed on long record showing (A–B) successive effects of myocardial depression by chloral hydrate; B–C, rapid infusion of 150 ml saline solution Intravenous dose of ouabain as indicated. Upper curve, mean atrial pressure, middle curve, diastolic and systolic changes of ventricle, lower curve, arterial systolic and diastolic pressures Curves to right, tracings of volume curves recorded on rapidly moving paper at A, B, C, and D

atria Recent studies suggest that changes of the elastic relaxation forces during the rapid inflow phase (improperly designated as *suction*) should be added to them.

CURRENT EVALUATION OF THE APPLICABILITY OF THE FRANK-STARLING LAWS IN THE CONTROL OF STROKE VOLUME AND WORK

There is a growing opinion among investigators that, while Starling's law is valid for the exposed isolated heart, a variety of factors operate in the body which minimize or nullify its importance as a regulator of cardiac output and work under physiologic conditions It follows that Starling's law is largely operative under extreme and unphysiologic conditions It is the author's opinion, based on his experiences as well as on current research, that *the postulates of Frank and Starling do apply to the mammalian heart in health and disease.* One might indeed inquire, as Harvey did, why nature would have provided a demonstrable mechanism if it is never used Within limitations of pericardial space, the response to diastolic stretch produced by changes in end-diastolic pressure normally dominates stroke volume when the sinus rate alters or moderate variations in venous return are concerned It is *the local intrinsic mechanism by which the heart adjusts to circumstances that do not require an alarm call for the assistance of nervous or hormonal regulatory mechanisms* The data also show that the Frank-Starling laws can be harmonized with Henderson's concept that cardiac output is largely controlled by changes in heart rate, however, it is possible for stroke volumes to increase during cardiac acceleration when venous return is augmented, as in exercise.

It must be emphasized, nevertheless, that the operation of the heart is dominated by these laws only when the inherent reactive capacity of the myocardium remains the same. Accumulating experimental and clinical evidence now favors the view that the inherent condition of the myocardium alters easily, not only in disease but also in physiologic states which occur in everyday life However, there is reason to believe that even in the presence of such changes, the laws of initial length and tension continue to operate silently, improving the stroke volumes even when their operation remains obscure

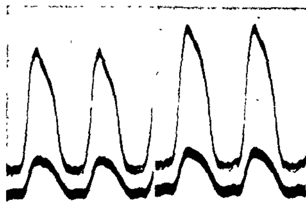


Fig. 2-36. Two segments of left ventricular (upper) and right ventricular (lower) pressure pulses taken before and after saline infusion to demonstrate increase in end-diastolic pressure in both ventricles

are extremely dilated and their contractions become very weak and infrequent, restoration of artificial respiration is followed by extremely vigorous beats. As illustrated in the right half of Fig 2-35, this results in marked reduction in residual volume as well as in diastolic size. It also gives an idea as to the extreme variations in residual volume that can take place as a result of altered physiologic conditions of heart muscle.

The Pericardium as a Limiting Factor. The question has often been raised as to the extent to which the pericardium normally limits ventricular expansion and thus prevents the operation of Starling's law. Measurements of pericardial space in cadavers and in living dogs (Fineberg) indicate that it is adequate to increase diastolic volumes of the ventricles sufficiently to permit doubling of the stroke volume at a heart rate of 80 per minute or above. However, the reserve capacity diminishes progressively as the heart rate slows, and at a rate of 40 per minute, the heart practically fills the pericardial sac. It is also possible that the pericardium may prevent operation of Starling's law in other physical ways. For example, Wilson and Meek (1927) concluded that a supradiaphragmatic accumulation of fluid causes the lateral pericardium to pull upon the heart, thus reducing the capacity of the right atrium. This could impair right ventricular filling and outcause this chamber to occupy a disproportionately larger part of the available space and thereby prevent adequate filling of the right heart (Hamilton and Remington, Berglund et al.).

Because of evidence that ventricular expansion is thus limited in well-filled hearts beating around seventy times per minute, the question is being revived whether changes in initial tension rather than length may not play a determining role. In postulating his concept, Frank, as well as his supporters, was, of course, aware of Laplace's principle that the tension on muscle fibers varies as the product of cavity pressure and radius of a sphere. They scarcely considered it important to belabor this elementary physical principle, as subsequent writers have felt impelled to do. The crucial point of the concept that *end-diastolic pressure is the ultimate determinant of the magnitude of an all-or-none response* has often been misunderstood, it is that changes in neither initial tension nor initial length of myocardial fibers are induced otherwise than through the force exerted by increased intracavity pressure. An inherent capacity of the ventricles to alter their diastolic size, that is their tonus, has not been demonstrated. True, after dilatation of the ventricles is once induced, the actual increment of end-diastolic pressure would be small. In fact, it could be so small that it might be undetectable on ventricular pressure pulses recorded by manometers of inadequate sensitivity such as are in common use at the present time. However, if ventricular dilatation is indeed restricted by the pericardium, *the elevation of end-diastolic pressure should become more pronounced.* This may explain why the author, who recorded pressure tracings of much larger amplitude from the heart within the pericardium, was able to detect changes in end-diastolic pressure whereas other investigators failed to do so. As an example, Fig 2-36 shows an elevation of end-diastolic pressure in both ventricles following saline infusion, and a similar elevation of end-diastolic pressure in the left ventricle can be observed following aortic compression.

As pointed out in 1928, end-diastolic ventricular pressure may be increased otherwise than through increased inflow volumes. It may, for instance, be elevated through less efficient ejection during previous beats, by more rapid isometric relaxation and an extension of filling time, and by more vigorous contractions of the

Therefore, none of them can vibrate without producing movements or vibrations in the blood which they contain Therefore, the cardiac walls, the valves, the arterial walls, and the blood represent an interdependent system which vibrates as a whole (Rushmer, 1955). On the other hand, studies of intracardiac phonocardiography (Luisada and Liu) prove that the sounds created in one chamber are only poorly transmitted to the others

As shown by Rushmer, the vibrations of the cardiovascular system are caused by

1 Acceleration or deceleration of the blood (*heart sounds*)

2 Turbulence of the blood (murmurs)

In an elastic chamber filled with fluid, any sudden motion throws the whole system into vibration, the momentum of the fluid causing an overstretch of the elastic walls, followed by a recoil and a displacement of fluid in the opposite direction.

The *intensity* of a sound seems to be proportional to the rate of change of the velocity of the blood, while the *frequency* of the sound seems to be connected with the relationship between vibrating mass and elasticity of the walls In the heart, the combined mass (walls plus blood) is very large in relationship to the elasticity. Therefore, the sounds have a relatively low frequency (Rushmer)

First Sound. The mechanism of production of the first sound has been repeatedly investigated Various factors have been considered important, but there has been no agreement, so far, in regard to the part played by them

Many authors believed that the first heart sound was chiefly due to a muscular vibration Confirming previous studies, Wiggers and Dean (1917) and Eckstein (1937) recorded sound vibrations produced by the contraction of an isolated, perfused strip of myocardium Kountz, Gilson, and Smith (1940) eliminated valvular action by clamping the venae cavae or by blocking the atrioventricular orifices A loud first sound was recorded over the cardiac wall until heart failure set in

It is interesting to note that the same type of experiments led others to believe that the first sound is due purely to a valvular factor Dock (1933) found that following ligation of the atrioventricular groove or of the venae cavae and the azygos, there was either disappearance or extreme reduction of the first sound, and concluded that the latter is due to "the sudden tension of the previously slack fibers of the AV valves"

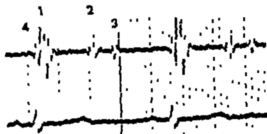


Fig. 2-37. The four heart sounds of a normal young person.

Smith, Essex, and Baldes (1950), on the basis of experiments on surviving, perfused dog hearts, reached the conclusion that the first sound is largely due "to the forceful striking of the valves." Still others believe that the first sound is caused by several factors. Orias and Braun-Menendez (1939), working with the Wiggers-Dean capsule in man, reached the conclusion that the first sound consists of separate vibrations caused by the atrial, valvular, muscular, and vascular factors Rappaport and Sprague (1942) confirmed these findings by means of a "stethoscopic" microphone Wiggers (1949) stated that ". . . the sudden elevation of intraventricular pressure produced by contraction sets many structures into vibration," although he denied that "vibrations of different structures maintain their identity and can be identified in heart sound records."

These contradictions are due to different and, at times, inadequate techniques. A recording funnel or lever applied directly over the myocardium does not adequately record sounds from the rest of the heart, while contact with a moving surface may cause artifacts Mechanical and optical systems for recording heart sounds are not sensitive enough and do not reproduce all the characteristics of the sounds accurately The physical characteristics of microphones and amplifiers may mar the result

A study on the mechanism of production of the first sound was made by the authors with Lewis (1952) The experiments were performed on rabbits and dogs under anesthesia and with open chest The mechanical activity of the heart was recorded (1) by introducing the heart through the hole of a rubber membrane into a glass cardiometer and recording the volume changes of the heart by means of a "linear" microphone, (2) by introducing a catheter into the left ventricle either via the left carotid artery or through the left atrial appendage and recording pressure changes The heart sounds were recorded by means

I

The heart sounds

Anatomic Basis

RICHARD H. LICATA

Physiologic Considerations

ALDO A. LUISADA AND MARIANO M. ALIMURUNG

ANATOMIC BASIS

Heart sounds result from the interplay of the dynamic events of blood flow and the operation of the valvular mechanisms The rate of flow of blood passing through the heart is sequentially altered according to the physiologic conditions of the cardiac chambers traversed During each phase of the cardiac cycle, the main directional mass movement of blood through the cavities of the heart and great vessels is determined and maintained as a function of the valvular apparatus The obvious interdependence of hemodynamic and valvular systems is influenced to some extent by the elastic properties of the heart wall The unison of function of these two systems results in a generation of *vibrations* emanating from the pulsating heart, and the resultant energy vectors produced are transmitted to particular points of reference along the chest surface, where they are interpreted as heart sounds or murmurs. The degree of audibility of these phenomena is greatly dependent upon the quality of the interposed transmitting medium For example, such vibrations are most easily lost in the regions insulated by the compressible mass represented by lung tissue or such areas of the mediastinum lodging accumulations of fat. These soft tissues cause a damping effect which results in poor transmission of sound to the surface of the thorax Vibrations are transmitted clearly and more directly through relatively solid tissues or layers of minimal thickness, thus resulting in a less attenuated sharpness of heart sound, which may consequently be picked up more readily on the chest surface The tendency for accumulation of fat within the tissues of the pericardial sac and the sulci of the epicardial surface must be considered as an added damping device, giving rise to variations in sound phenomena.

Four principal foci of maximum intensity are normally mapped on the chest wall While these localizations result from vibrations emitted at the level of the four major valves, they do not correspond directly in anatomic position to these structures but lie along relatively widely divergent lines over the chest wall. These points apparently represent the most effective pathways of transmission for the vectors of vibration from their original sites, which are subsequently translated into sound on the precordium

PHYSIOLOGIC CONSIDERATIONS

Normal mammalians present two heart sounds by auscultation However, graphic tracings may reveal up to four sounds (and occasionally more) (Fig 2-37). The two louder sounds are called the first and second, the others, the third and fourth (see also Part 3, Chap 9, Phonocardiography).

The cardiac chambers are filled with blood

a. A slow initial vibration = tension
b First rapid vibration = closure of mitral valve, *M*
c Second rapid vibration = closure of tricuspid valve, *T*
d Third rapid vibration = opening of pulmonic valve, *P*
e. Fourth rapid vibration = opening of aortic valve, *A*
f A few slow final vibrations = flow into the large arteries

The normal sequence of valvular events outlined above has been confirmed by Braunwald and Morrow (1958) and others. Studies of intracardiac phonocardiography confirm these data. Closing of the mitral valve is revealed by a rapid left ventricular vibration which precedes a similar vibration within the right ventricle (Fig. 2-39). Opening of the pulmonic valve (vibration in the right ventricle) precedes opening of the aortic valve [vibration in the left ventricle (Fig 2-39)].

The explanation of the slow initial vibration of the first sound is based on the fact that it follows the peak R of the ECG and slightly precedes the rise of pressure in the left ventricle The explanation of the final slow vibrations is based on their coincidence with the ascending branch of the aortic and pulmonic pulses.

Smaller vibrations, possibly of *muscular nature*, may be seen in certain tracings between the two main groups of vibrations of the first sound but usually have a secondary importance *Vascular vibrations* occur later, after the be-

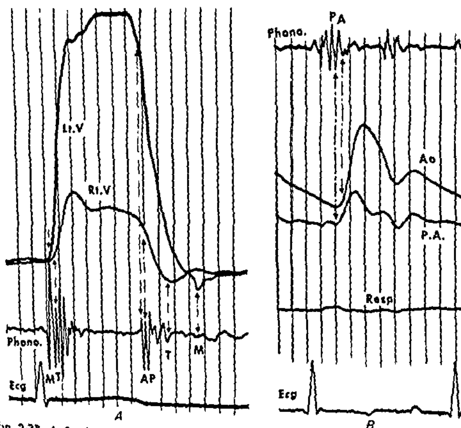


Fig 2-38. A Simultaneous pressure tracings from the right, *Rt. V*, and left, *Lt. V*, ventricles of a dog, with a phonocardiogram at apex, *Phono*, and electrocardiogram, *Ecg* Within the first sound, *M* and *T* indicate closure of the mitral and tricuspid valves. Within the second sound, *A* and *P* indicate closure of the aortic and pulmonic valves Later, *T* and *M* indicate the opening of the tricuspid and mitral valves B Simultaneous pressure tracings from the aorta, *Ao*, and pulmonary artery, *P.A*, of a dog, with a phonocardiogram at the apex, *Phono*, an electrocardiogram, *Ecg*, and a tracing of respiration, *Resp* Within the first sound, *P* and *A* indicate the opening of the pulmonic and aortic valves

of a "stethoscopic" microphone connected with the outlet of the cardiometer. In this manner, the sounds were collected from the entire cardiac surface and transmitted through the air contained in the cardiometer while contact of the beating heart with the wall of the cardiometer itself was avoided.

Several types of experiments were performed, and records of the heart sounds were taken:

1. From the empty heart (ligation of the veins, opening of the arteries)
2. After prevention of valvular movements by a ligature around the AV groove
3. After damage to both AV valves causing severe insufficiency
4. After ligation of the large arterial vessels
5. After myocardial necrosis

The first group of experiments demonstrated that *when all inflowing channels are closed and the heart contains only air, the amplitude of the first sound is reduced out of proportion with that of the ventricular contraction.* The separation of the ventricles from the other chambers leads to the disappearance of the first sound in accordance with the results of Dock and contrary to those of Kountz and coworkers (possibly the first sound persisted in the experiments of the latter because complete emptying of the heart or complete separation of the atria from the ventricles was not obtained). Other experiments demonstrated that *extensive damage of either the AV valves or the ventricular walls causes an extreme reduction in the intensity of the first sound, out of proportion with the amplitude of the ventricular contractions*

It was concluded that *it is impossible to separate muscular from valvular factors* The manner in which the valves close and open depends upon changes in atrial and ventricular pressures, due in turn to muscular contraction, on the other hand, any change in the function of the valves results in modification of the contour of the pressure curves. In spite of this difficulty, one may *estimate the relative importance* of the ventricular and muscular factors in the determination of the first sound. The results of the experiments on the empty heart show that the sound vibrations due to the myocardial contraction per se are extremely small, and while Eckstein proved that a contracting strip of heart muscle is capable of giving sounds, these occur only at the beginning of contraction, when there is a sudden change of tension. *No appreciable vibrations are recorded during most of the ventricular systole.* This alone should indicate that the importance of a muscular factor per se is secondary. Even though the vibrations of the first and second sound coincide with the closing and opening of the valves, it should be kept in mind that they correspond primarily to harmonics of the sudden changes in pressure which take place in the cardiac chambers and in the cardiac walls.

During the early part of a normal ventricular contraction, two mechanical events take place. The first, occurring at the beginning of systole, consists of *sudden tension of the ventricular walls* with rise in the ventricular pressure and closure of the AV valves. The second, which follows immediately, is caused by opening of the semilunar valves, and is accompanied by a *sudden vibration of the ventricular walls.* Emphasis of the higher-pitched vibrations is obtained in the phonocardiogram by filtering out the low frequencies and amplifying the others The lower-pitched vibrations, on the other hand, are recorded in the low-frequency tracing simply because they are larger; the sonic vibrations are relatively minimized because there is no need of large amplification.

The mechanical events taking place at the beginning of systole were revealed in the sound tracings of the past by *two* large vibrations However, studies by Luisada et al. (1958) in dogs and human beings, with a highly sensitive microphone and a cathode-ray oscilloscope, have revealed *four* vibrations. Double catheterization of normal dogs under chloralose anesthesia has revealed the following facts·

1. There is a slight difference in the rise of pressure between left and right ventricles: the left is steeper and starts slightly earlier than the right. The left ventricular rise (closure of the mitral valve) coincides with the *first* vibration of the first sound, the right ventricular rise *(closure of the tricuspid valve) coincides* with the *second* (Fig. 2-38A)

2 There is a slight asynchronism in the rise of pressure between pulmonary artery and aorta· the *PA* rise occurs earlier and coincides with the *third* vibration of the first sound; the *Ao* rise occurs slightly later and coincides with the *fourth* vibration of the first sound (Fig 2-38B). Therefore, the following events can be seen within the first sound complex:

the last theory. Revival of the concept of *active diastole* of the ventricles might lead to speculation that the sound takes place at the maximum of this phase or at the time of its cessation. Luisada (1952) observed splitting of the third sound in clinical cases. Experiments in dogs reveal that rapid filling takes place much *earlier in the right than in the left ventricle* (Fig. 2-39A). In clinical cases, a third sound due to the left ventricle is usually heard or recorded at the apex while a third sound due to the right ventricle is heard or recorded at the epigastrium or at the midprecordium.

Fourth Sound. This sound takes place in presystole and is due to vibrations of the ventricular walls which occur when blood is forced into the ventricles by atrial contraction. Comparison of the fourth sound recorded by way of the esophagus with that recorded at the apex revealed that while early vibrations of the esophageal tracing could be attributed to the atrial contraction per se or to valvular vibrations, the vibrations recorded at the apex occurred later and could be explained only with ventricular vibrations (Orias and Braun-Menendez, 1939).

As right atrial contraction slightly precedes left atrial contraction, a double fourth sound may be recorded in clinical cases (Luisada, 1952).

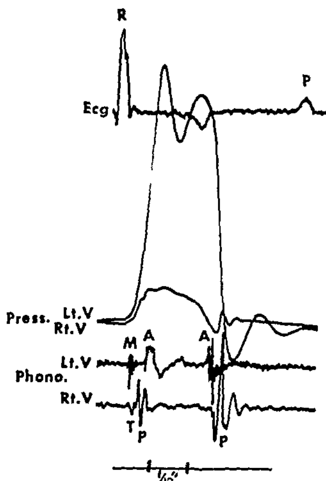


Fig. 2-39. Simultaneous pressure tracings from the left, Lt V, and the right, Rt. V, ventricles of a dog Also, simultaneous intracardiac phonocardiograms, Phono, from the left, Lt V, and right, Rt. V, ventricles. In the left ventricle: closure of mitral valve, M, opening of the aortic valve, A, closure of aortic valve, A. In the right ventricle, closure of tricuspid valve, T, opening of the pulmonic valve, P, closure of pulmonic valve, P.

ginning of ejection, and can be easily recognized because they are usually lower pitched.

In conclusion, in spite of the existence of multiple factors and the fact that vibrations arise in multiple structures, the first heart sound has four clearly visible phases which coincide with the main valvular events taking place in early systole.

Second Sound. The second sound, as clinically heard, is caused by the closing of the semilunar valves of the aorta and pulmonary artery. However, subsequent vibrations coinciding with the opening of the AV valves may be seen in graphic tracings and may, in certain cases, either prolong the sound or become audible as a separate sound.

Experimental studies of Luisada et al (1958) have shown that the incisura of the *pulmonic pulse takes place after that of the aortic* pulse (Fig. 2-38B). This indicates that whenever two large vibrations are visible within the second sound, the first is aortic, the second pulmonic. This confirms clinical observations of Leatham (1954).

The *opening of the AV valves,* according to the same study of Luisada et al. (1958), is also nonsimultaneous (Fig. 2-38A). Opening of the tricuspid valve precedes that of the mitral valve. This explains occasional multiple vibrations which can be observed in early diastole between the second and third sounds.

Third Sound. The third sound is a dull sound which may be heard at the apex of normal children or adolescents and either at the apex or epigastrium of cardiac patients.

Two alternative theories have been advocated. The first, advocated by Thayer (1909) and by Dock (1956), attributed this sound to a vibration of the mitral valve, other authors attributed it to an impact of the apex on the chest wall A second theory explained it as due to *vibrations of the ventricular walls at the time of rapid filling* on account of the onrush of blood from the atria to the ventricles. The perfect coincidence between the third sound and the peak of the phase of rapid filling, both in animals and in human beings, seems to confirm

TABLE 2-2 TIME INTERVALS BETWEEN PHASES OF HEART SOUNDS IN NORMAL DOGS

Sound	*Sequence of vibrations*	*Interval between vibrations, in sec*
Fourth	Right atrial Left atrial	0 03
First	Closure mitral Closure tricuspid Opening pulmonic Opening aortic	0 02 0 02 0 02
Second	Closing aortic Closing pulmonic Opening tricuspid Opening mitral	0 02-0 03 0 01-0 02 0 02-0.06
Third	Rapid filling (right) Rapid filling (left)	0.03-0 08

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II

The vascular system

WILLIAM F. HAMILTON

The vascular system is in many respects the most complex, intricate, and important part of the circulatory apparatus. It consists of a system of branching tubes, miles in aggregate length, and intricately connected. They are beautifully regulated to serve the body with materials for nutrition and respiration, and also to carry off wastes to the organs of final disposal.

The vascular system may be divided into three parts The first is the *distributing system*, which consists of the arteries and arterioles which *transport* the blood to the organs of the body and *regulate* the supply of blood to the needs of the several organs. The second is the *diffusing system*, which consists of the capillaries, each a thin-walled tube a fraction of a millimeter long and a hundredth of a millimeter in diameter The walls of these vessels are so thin that they permit the diffusion of carbon dioxide, oxygen, and wastes to nearly complete equilibrium in the fraction of a second during which the blood passes through them. The capillary walls are, in spite of this thinness, so strong that they can withstand the systolic arterial pressure without damage (as when the physician slowly reduces pressure in a blood-pressure armlet). The third functional part of the vascular apparatus is the *collecting system* The veins drain all the capillaries and, in distensible tubes, carry the blood back to the heart.

Looking at the circulation from a slightly different viewpoint, one can think that it consists of *two elastic reservoirs*, a high-pressure distributing reservoir and a low-pressure collecting reservoir, and can think that the heart is a pump which is regulated by clever servomechanisms to maintain pressure in the distributing reservoir at a reasonably constant level. The variability in the capacity of the two reservoirs is of great functional importance

The *arterial, or high-pressure, reservoir* suffers its most important capacity changes passively—distention by pressure from within. Thus when the heart contracts, expelling some 80 ml of blood into the aorta, there is an increase of 40 mm Hg in arterial pressure (pulse pressure). The fact that between beats, arterial pressure is maintained at a level that normally stays between 60 and 80 mm Hg ensures that *continuous rather than intermittent flow* shall perfuse the tissues. Minor capacity changes of the large arteries are due to active contraction of the wall.

The *low-pressure reservoir* is a complex functional concept rather than a simple structural one. It contains all the blood mobilized for pumping by the left ventricle. Such blood is contained in the ventricles during diastole and in the atria during the entire cycle (There is clear evidence that, under extreme stress, at least one-fifth of the total blood volume may be stored in the heart—Hamilton et al., 1950) In addition, the low-pressure reservoir comprises the whole of the lesser circulation, the great systemic veins, the sinuses of the liver, and the pulp of the spleen

The function of this reservoir is to ensure venous return adequate for left ventricular pumping and thus to make up for blood that goes to active organs when their small blood vessels are dilated In order to serve this function, the low-pressure reservoir must diminish

in capacity when the great muscle masses are active and require a large blood flow and hence have a large blood capacity. The size of the venous reservoir is diminished by different mechanisms in its different parts The *small veins* have muscular walls which are capable of constricting but not tightly enough to hinder their flow The *larger veins* can also reduce their capacity by active constriction. The veins from the gut, for example, can, by constricting, reduce content by 10 to 20 per cent of the total blood volume contained in this organ (Alexander, 1954a). The peripheral veins, particularly those equipped with valves and draining the limbs, are also emptied of their blood by the activity of the overlying muscles and by the movements of the joints which stretch segments of the veins This venous pump, responding as it does to the small movements involved even in balancing, prevents the accumulation of blood in dependent veins

The *spleen*, in the dog at least, is capable of active contraction and can release large amounts of concentrated blood into the circulation (Barcroft) Change in the capacity of the *great central veins* and the *pulmonary vasculature* is active in the sense that the walls of these vessels constrict and thus reduce their capacity, again without greatly increasing resistance to flow. It is probable, however, that a great deal of the change in capacity of these parts of the great low-pressure reservoir is the passive result of changes in distending pressure wrought by changes in the pumping of the heart and by changes of the systemic arterioles

Changes in the *storage capacity of the heart* complement the changes in storage capacity of the veins and, in the normal animal, depend greatly upon the rate of the heart. The more time for cardiac filling, the larger the heart, as is illustrated by the fact that when heart size in the normal animal is correlated with stroke volume, stroke work, or lapse of diastolic time, only the last of these variables shows any clear correlation This fact is, of course, meaningless when the heart rate is held constant, as in a Starling heart-lung preparation, and is nearly so when the heart rate is continuously rapid, as in heart disease or in the open-chest carcass, a widely used experimental preparation

The low-pressure reservoir is thus seen to be able to change its capacity to a very marked degree and to make up for the blood required elsewhere by vasodilatation and still assure the delivery of blood to the heart at adequate pressure and in adequate amounts to cover all physiologic variations in cardiac output

It is remarkable that *sympathetic activity* tends to reduce the capacity of the several parts of the low-pressure reservoir. The veins are known to constrict, the spleen to contract, and the heart to accelerate under this influence. Acceleration of the heart reduces its size, even though cardiac output increases, as in exercise

During exercise, the small arteries of the muscles dilate *in response to chemical stimuli* connected with the increased muscular metabolism This occurs in spite of vigorous sympathetic innervation which is free to reduce the capacity of the low-pressure reservoir, as seen above, thus freeing blood to fill the dilated vascular bed in the active organ

The blood vessels thus consist of a servomechanism whose activity in regulating the rate of the circulation and its distribution to meet the ever-varying needs of the several organs of the body is of the utmost importance. This mechanism complements the mechanism which regulates the heart, and together the two mechanisms maintain the blood pressure nearly constant in the face of a tenfold or greater variation in the output of the heart In this regulation, the primary fact is that in the state of normal health, there is an ample supply of blood at the portals of the heart. This is in sharp contrast to the situation obtaining in a "physiologic" preparation subjected to severe surgical intervention, in which the blood volume is so reduced in relation to the capacity of the venous reservoir that the return of blood to the heart is subnormal even in the inactive supine state Such an animal could not support any muscular activity, and yet it is thought of as "normal" by some physiologists.

Peripheral Resistance. The basic relationship for understanding peripheral blood flow is that between resistance, pressure, and flow Resistance is conventionally defined in terms of pressure and flow as $R = P/F$ This means in practical terms that vasoconstriction, which may either raise the pressure (if widespread) or reduce the flow (if local), brings about either a widespread or a local increase in resistance Vasodilatation does the opposite of these two things and brings about either a widespread or

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smallest tubes unless the velocity is reduced in equal proportion to the cross area. The velocity of flow through a system of branching tubes is inversely proportional to the aggregate cross area at any level The sum of the cross areas of two daughter arteries is somewhat greater than that of the parent arteries, and the velocity of flow somewhat slower, but the anatomic relation is such that the velocity is maintained in the *precapillary arterioles*, so that the greatest pressure drop occurs there

Each arteriole branches into many *capillaries*, which form a *complex pattern of direct* "thoroughfare channels" and secondary "loops," whose aggregate cross area is many times the cross area of the arterioles Therefore, the velocity of flow becomes much less The pressure drop from end to end of the capillaries is hence much less than that across the arterioles

As the *venous tributaries* coalesce into the venous plexus, *a narrowing of the* channel and an *acceleration of flow again occur, but never* enough *to make a significant pressure drop* over the venous system.

The dimensionally exact statement of Poiseuille's law, as given above, is an analogy *rather than a quantitative description of the circulation*. The dimensions of the small vessels are unknown, various, and changing *The viscosity* of blood is anomalous. Moreover, the total number of open blood vessels is known to vary Pressure *measurements* and velocity estimations can be made, but *one is far from a* dimensional analysis of the relationships in the natural circulation

Thus the precapillary *small arteries, or arterioles*, are the *site of the* peripheral resistance and of its regulation Some authors (Zweifach, 1949) emphasize *the role of* precapillary *sphincters* as against the constriction of the arteriole as a whole

The mechanisms involved in the regulation of resistance by vasoconstriction and dilatation may be divided into two categories (1) local mechanisms that serve the immediate *needs of* the tissues, and (2) general mechanisms that participate in the regulation of blood pressure and the dissipation of heat

The *local mechanisms* are *chemical* and nervous The *chemical* mechanisms bring about vasodilatation as a *result of* lessening oxygen supply (reactive hyperemia) or of increased metabolic activity of the organ *This* will occur in the absence of nerve supply as well as in its presence This response tends to keep the AV oxygen difference constant in muscle, skin, viscera, heart, and brain. The *response of the* pulmonary vasculature is just the opposite When hypoxic blood passes through the lungs, no effect is seen, but when the lungs are ventilated with extremely low oxygen mixtures, increased resistance occurs (von Euler, 1946; Wiggers, 1950b).

The *local nervous mechanisms are of two* kinds, true *reflexes and axon reflexes*. Certain afferent nerves, such as the auricular nerve of the rabbit, can be stimulated so as to produce a reflex local hyperemia These observations were made long ago (Bayliss, 1902) and should be repeated *Axon reflexes* result in localized dilatation, for example when the skin is irritated (Bruce, Lewis). The dilatation is *not due to a* true *reflex, because it will* occur when the *afferent nerve from the part has been recently* cut or blocked but not in parts whose afferent nerve supply has degenerated The mechanism may be activated centrally by *reflexes, by* electrical stimulation of the *dorsal* roots, or by disease of the dorsal ganglia (herpes). Axon *reflexes* have been *suggested* as the cause of *hyperemia following* intestinal manipulation *and as the cause* of arteriolar constriction which *is said* to result from venous distention or inflammation.

In competition with the local control of blood flow for the needs of the active organs are the body-wide reflexes which, by constriction and dilatation, control the blood pressure and heat *dissipation*

The reflexes which control arterial *pressure* can be divided into two classes, the *anticipatory* and the *regulatory* The former are active during the excitement *which precedes* activity and include increased general sympathetic tone, vasoconstriction *in* the skin and in the less active viscera, the secretion *of* epinephrine, and the dilatation of skeletal muscle *arteries* *This* anticipatory response is made more active by *cutaneous* pain and *emotional* responses, such as fright and anger.

The regulatory blood *pressure* reflexes control not *only* the heart *but also the* peripheral resistance. *These reflexes* take origin in the *stretch receptors of the* aortic arch and carotid sinus They are bulbar *reflexes* and are activated by *a rise in* blood pressure These re-

local drop in resistance and a local or widespread increase in flow.

Resistance is expressed in absolute dimensional terms as:

$$R = \frac{\text{dynes/cm}^2}{\text{cm}^3/\text{sec}} \qquad \text{or dyne sec cm}^{-5}$$

where the numerator is the pressure drop from artery to vein, and the denominator is the flow. An equivalent expression is:

$$R = \frac{Pa - Pv \text{ in mm Hg} \times 1\,332}{\text{flow in cm}^3/\text{sec}}$$

The relationship expressed here has dimensional meaning when the fluid is a perfectly viscous (newtonian) fluid and when the walls of the tube are rigid. Its application to blood in the vascular system is only approximate. This is because the blood vessels are distensible and the viscosity of blood is anomalous. Blood has nearly the viscosity of plasma when it is flowing rapidly and the cells take a central course through the vessel with plasma absorbing the frictional forces near the vessel wall. In an ordinary viscometer, blood has the viscosity of a mixture of cells and plasma.

The fact that the blood vessels are distensible leads to a reduction of resistance when pressure is increased. These relations can be diagramed as in Fig. 2-40 The highly distensible pulmonary vessels carry the tendency to an extreme. Here the blood flow may double with hardly a perceptible rise in pulmonary arterial pressure There is a limit, however, to the resistance drop which can result from distention with minimal pressure rise. With increased pulmonary flows, as in left-to-right congenital shunts, pulmonary hypertension will result from a fourfold increase in flow, P_1 Restriction of the pulmonary vascular bed, as after pneumonectomy or in destructive pulmonary disease, will give rise to pulmonary hypertension with small increases in flow or with normal flows P_2 When the lungs have been subject to chronic increase in either flow (septal defect) or back pressure (mitral stenosis), proliferative changes occur in the arterioles which result in increased precapillary resistance, P_3.

In contrast, line A shows the relationship between pressure and flow which is described by *Poiseuille's law* in rigid tubes whose dimensions are known. Since the line crosses the origin, the relation of pressure to flow (i e., the resistance) is constant. According to Whittaker and Winton, a similar relationship holds for a dilated vascular bed perfused by a newtonian fluid (plasma), though, of course, it cannot be said that Poiseuille's law holds since the dimensions of the system of tubes are not known.

Line D shows the relation seen in a dilated vascular bed, in which an increase in pressure has little effect on resistance and in which flow comes to a halt at finite pressure levels. This cessation of flow, according to Whittaker and Winton, is due to the presence of plastic blood cells and comes at higher pressures when there are more cells. Burton (1951), on the other hand, believes that the flow stops in small vessels capable of obliterating their lumens because, as the pressure decreases, the elastic tension in the walls of the small vessels works at a greater mechanical advantage as the vessel becomes smaller and the curvature of its wall becomes greater (Laplace). Thus for each vessel, there is a "critical closing pressure" at which the elastic-wall tension overbalances the distending force and closes the vessel. The question as to whether flow ceases at a finite pressure with newtonian perfusates is moot Line C indicates the pressure-flow relations which are said to exist in a constricted systemic arterial bed.

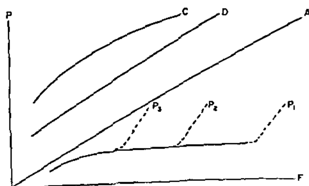


Fig. 2-40. Relationship between pressure and flow in distensible blood vessels and in rigid tubes For detailed explanation, see text.

The control of the peripheral resistance. The frictional loss of pressure, P, in a tube is equal to the product of resistance and flow:

$$P = RF$$

In terms of the dimensions of a rigid tube and the nature of the fluid.

$$P = \frac{8\eta Vl}{a}$$

where P is the pressure drop from one end of the tube to the other, η, the effective viscosity of the fluid, V, its velocity of flow, l, the length of the tube, and a, its cross area

The pressure drop is thus greatest in the

12

Cardiovascular and pulmonary reflexes[1]

ERIC NEIL AND CORNEILLE HEYMANS

PRESSORECEPTORS OF THE SYSTEMIC ARTERIAL SYSTEM

The following is a brief historical account of the discovery of the reflex regulation of the circulation

Following the proof of the circulation of the blood by William Harvey (1628), his pupil Lower (1669) studied the effect of venous pooling on the strength of the heart beat He was the first to use the term "venous tone" and recognized that pooling of the blood may occur in the veins, thereby decreasing the venous return It took nearly 200 years for anything fundamental to be added to this concept, for the existence of vasomotor nerves and their control of arteriolar caliber and venous capacity were not appreciated until 1851 and 1863, respectively The discovery of the sympathetic vasomotor nerves by Claude Bernard, Brown-Sequard, and Waller (1851–1853) stimulated interest in the mode of action of these nerve endings on the circulation However, the development of the graphic registration of blood pressure by Ludwig (1847), using his *kymograph*, greatly accelerated the discovery of the autonomic control of the circulation Ludwig and his pupils were thus enabled to examine the effects of sensory nerve stimulation on blood pressure Electrical stimulation of most sensory nerve trunks caused hypertension, but Cyon and Ludwig (1866) found that such stimulation of the central end of a nerve in the neck of the rabbit, which lay separate from the vagus and the cervical sympathetic trunk, caused profound bradycardia and hypotension Cyon an[illegible] which [illegible] afferen[illegible] induces [illegible] cardiac slowing and reflex diminution of vasoconstrictor activity They believed, however, that the depressor nerve arose from endings in the heart and correspondingly argued that these hypothetic cardiac endings were stimulated when the heart was beating under stress against an untoward arterial resistance It is fascinating to reflect that von Bezold and Hirt described the effects of veratrine 2 years later, in which bradycardia and hypotension were produced, it is now realized that veratrine artificially stimulates ventricular vagal receptors which normally subserve just such a function as Cyon and Ludwig envisaged for their depressor nerve endings

The localization of the medullary vasomotor center and the proof that the vasomotor center discharged via tracts in the anterolateral columns of the cord harmonized well with the observations of Bernard (1856) and Cyon (1871) that spinal transection in the cervical region caused a profound fall of blood pressure Ludwig and Thiry (1864) had also recognized that the splanchnic nerves, arising from the lower six thoracic segments, were of great importance in maintaining arteriolar resistance in the splanchnic bed, and Goltz (1864) in his famous *Klopfversuch*, proved how important a part splanchnic venous tone played in restricting the capacity of the circulation and thereby maintaining venous return

Cyon and Ludwig (1866) did not believe that the depressor nerves were tonically active, for bilateral section of these nerves did not alter the systemic blood pressure level. It is now known that the reason for the slight or negligible rise of blood pressure after depressor nerve section lies in the buffer activity of the sinus nerves which remain intact The function of these nerves was not appreciated until 1923 It had long been known that ligation or occlusion of both carotid arteries caused systemic hypertension, but this was ascribed to the effect of cerebral anemia on the medullary vasomotor center François-Franck (1877) and

[1] For complete bibliography, see Heymans and Neil, 1958

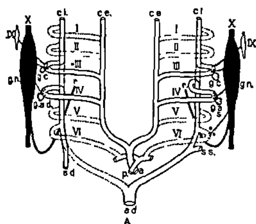
flexes result in stimulation of the vagus center and inhibition of the cardioaccelerator center, in stimulation of the vasodilator center, and in inhibition of the vasoconstrictor center. Their control is accurate and flexible, so that large changes in flow may occur with small changes in pressure.

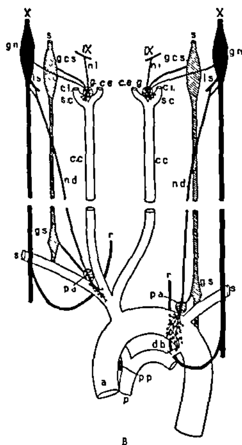
The circulatory control of heat dissipation involves cutaneous constriction in the cold and cutaneous dilatation in warm weather. These responses are controlled by the hypothalamus, which acts through the vasoconstrictor and dilator center and is the central mechanism for coordinating visceral and somatic function. The constriction conserves heat by keeping the warm blood away from the surface of the body, while the dilatation brings the warm blood to the surface where heat may be lost.

Many arteriovenous anastomoses are seen in the rabbit's ear, the toe pads of most animals, the human hands, feet, and face. These parts are important in dissipating heat. It seems likely that heat loss is served by the opening of the arteriovenous anastomosis, increasing the total flow and heat transport to the part, but that capillary flow is regulated by the metabolic needs of the tissues.

Activity increases heat production and hence the need for heat dissipation. Activity thus makes a double demand on the circulation Blood is required for transport of oxygen to the active muscles and of heat to the skin.

In summary, the vascular system controls the circulation by responding with great delicacy to the demands of active organs for oxygen and of the hypothalamus for the dissipation of heat. In health, the vascular regulation is such that an ample venous return is always ensured, even if the heart puts out ten times the resting flow. The action of the heart is reflexly augmented by a small fall in blood pressure and inhibited by a small rise. These responses, together with a similar control of the peripheral resistance, maintain a fairly constant pressure in the distributing reservoir despite changing demands.





the level of the origin of the superior thyroid artery in the cat. A branch of the vagus emerges from this region and runs to the vagus trunk, usually entering it in the vicinity of the nodose ganglion Green (1954) and Boss and Green (1956) have further described three or four pressoreceptor areas in the right common carotid artery, scattered between the origin of the superior thyroid artery and the root of the right subclavian artery. The pressoreceptor nerves from these areas are very fine and join the right aortic nerve.

Methods of Study of Pressoreceptors and Pressoreceptor Reflexes

Electroneurography. Chronologically, electrical recording of the pressoreceptor afferents should not be considered first, but most of the features of the sinoaortic reflexes can be more readily appreciated if the behavior of the pressoreceptor endings themselves is thoroughly understood.

Koster and Tschermak (1902), Einthoven (1908), and Adrian (1926) made early reports of electrical activity in the aortic nerves induced by a rise of aortic pressure, and the last two authors were fully aware that electrical changes occurred with each pulse. However, the anatomic advantages offered by the carotid sinus, which can be isolated from the general circulation and subjected to a variety of pressures (either static or pulsatile), has resulted in a more complete study of the sinus pressoreceptors There is, however, no reason to suppose that the nerve endings of the sinus behave in any way differently from those of the aortic arch. The sinoaortic nerves work as a functional entity, as was clearly recognized by Hering (1927) Bronk and Stella (1932) recorded the electroneurogram of the sinus nerve simultaneously with an optical record of the blood pressure *They noted that a burst of impulses occurred with each pulse* The nerve was then

Fig 2-41. A Scheme of innervation of the aortic arches in the embryo mammal X, Vagus nerve, IX, glossopharyngeal nerve, c i, internal carotid, c e, external carotid; g c, carotid glomus, g a d, right aortic body, g a s, left aortic body, r, recurrent laryngeal nerve; s s, left subclavian, s d., right subclavian, a d, dorsal aorta, I, II, III, IV, V, VI, aortic arches, a, aortic arch, p, pulmonary artery, g n, nodose ganglion of vagus B Scheme of innervation of the receptor areas in the aortic and sinus regions in the adult rabbit X, Vagus, *s*, sympathetic, *g.c s*, *superior cervical* ganglion, g n, nodose ganglion, *l s*, superior laryngeal nerve, g, carotid glomus, n.i, sinus nerve, c i, internal carotid artery, a, aorta, *c e*, *external* carotid artery; *p*, pulmonary artery, IX, glossopharyngeal nerve; c c, common carotid *artery*, *n d*, depressor (aortic) nerve, g s, stellate ganglion, s c., carotid sinus, p p, pulmonary paraganglion; *p a.*, *aortic* paraganglion, r., recurrent laryngeal nerve, d b, ductus Botalli. (From *Muratori*, 1937.)

Hédon (1910) induced bradycardia by raising the blood pressure in the perfused carotidocephalic circulation and again ascribed the response to a direct effect of the blood pressure on the medullary cardiac center. Even as late as 1925, Anrep and Starling wrote, "a mechanical rise in the blood pressure in the brain inhibits the vasomotor center and stimulates the cardioinhibitory center."

Although Pagano (1900) and Siciliano (1900) cast doubt on the then classical interpretation of the mode of action of carotid occlusion on the blood pressure, their prescient suggestions were unfortunately refuted by Kaufmann (1912) and Kisch and Sakai (1923). It was left to Hering (1923–1924) to show that the carotid bifurcation was a reflexogenic zone. Hering stimulated the central end of the carotid sinus nerve and evoked bradycardia and hypotension. Similar reflex responses were obtained by mechanical stimulation of the carotid sinus itself, all these responses were abolished by cutting the sinus nerve. Hering noted that bilateral sinus nerve section caused systemic hypertension He realized that the sinoaortic nerves were a functional entity and christened them *Blutdruckzügler*, adumbrating their tonic activity in the normal circulation

Anatomy

Aortic Nerves. The depressor nerves, shown first in the rabbit, exist in other species but are not commonly separate from the vagal trunk. Koster and Tschermak (1902, 1903) and Tello (1924) proved beyond doubt that the nerve endings lie in the aortic arch and in the walls of the brachiocephalic and left subclavian arteries at their immediate origin from the arch itself. The most notable studies of the histology of the aortic arch pressoreceptors are those of Abraham (1941–1955). The sensory innervation is found in the adventitia only, the nerve endings are profusely distributed In view of the aortic origin of the nerve, the name "aortic" is preferable to "depressor," although the two are synonymous. In the cat, the aortic nerve contains some 450 fibers, two-thirds of which are myelinated The myelinated fibers have a bimodal distribution with peaks in the 2 to 4 μ and 8 to 10 μ diameter groups (Agostoni et al., 1957) Langley (1892) and Sarkar (1922) found myelinated fibers 4 to 8 μ in diameter in the aortic nerve of the rabbit, as well as nonmyelinated fibers. The presence of myelinated afferents (A fibers) and nonmyelinated afferents (C fibers) was inferred by Douglas et al. (1956) from action potentials of the aortic nerve in the rabbit.

Tigerstedt (1923) and Koch (1931) should be consulted for literature on the comparative anatomy of the aortic nerves. The left aortic nerve commonly leaves the vicinity of the vagus trunk above the annulus of Vieussens and passes behind or lateral to the left common carotid artery lying anterior to the trachea in the lower third of its course, to reach the anterior surface of the aortic arch. The right aortic nerve arises from the origin of the right subclavian artery (Tello, 1924). The cell bodies of the aortic nerve fibers are situated in the nodose ganglion of the vagus.

The Carotid Sinus Nerves. The *carotid sinus* is a dilatation of the internal carotid artery situated at the origin of the vessel Meyer (1876) and others drew attention to a thinning of the arterial wall in the carotid sinus, and De Castro (1926, 1928) showed that this could be recognized even in the newborn animal or infant. The *sinus nerve*, which is a branch of the glossopharyngeal nerve, was first described by Knoll (1885). De Castro (1926, 1928) described the extraordinary richness of the sensory innervation of the carotid sinus Details of the comparative anatomy of the carotid sinus are given by Heymans and Neil (1958).

Koch (1931) was the first to recognize the significance of the sites of the pressoreceptor areas in the adult mammalian circulation In more primitive animals and in the mammalian embryo, six visceral aortic arches develop, and each of them is probably provided with visceral afferent nerves carrying pressoreceptor impulses from the sensory innervation of the blood vessels In the mammal, the first and second visceral aortic arches disappear From the third arch develops the internal carotid artery, and its innervation by the glossopharyngeal nerve persists as the nerve of the carotid sinus. The fourth arch becomes the systemic aorta on the left side and the right subclavian artery on the right side, and the nerve of the fourth arch—the laryngeal branch of the vagus—forms the sensory innervation of these areas as the adult *aortic nerves* (Fig 2-41).

The Common Carotid Pressoreceptor Areas. Green (1953, 1954) has described a pressoreceptor area in the common carotid artery at

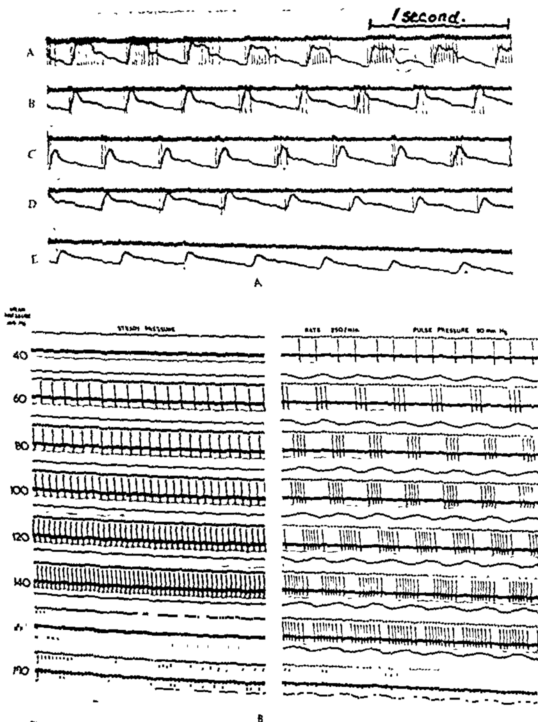


Fig 2-42 A Impulse activity in a single fiber of the left aortic nerve, and blood pressure recorded from the left common carotid artery Mean blood pressure, in millimeters of mercury, at A, 125; B, 80, C, 62· D, 55, E, 42 (From E Neil Arch Middlesex Hosp 1954) B Left, impulse activity in single pressoreceptor of common carotid nerve at different static pressures in the artery segment Right, impulse activity in single pressoreceptor of common carotid nerve during application of pulsations (250/min – pulse pressure 50 mm Hg) at different mean pressures Compare with figure on the left (From Green)

thinned by dissection, and a single active unit was obtained. The single unit fired with each systolic rise of blood pressure, and the impulse frequency was greatest during the systolic upstroke of the pressure wave. The impulse frequency fell off as the blood pressure dropped from its systolic peak, and often the firing ceased at a point on the pressure wave at which the pressure level was above that of the commencement of impulse discharge during the systolic upstroke (Fig. 2-42A). In accordance with the behavior of other mechanoreceptors, *the frequency of impulses from the pressoreceptors of the sinus is largely decided by the rate of rise of tension or stretch which affects it.* Different pressoreceptors have different thresholds, not only to steady pressure, but also to the rate of rise of pressure. Higher pressures in the sinus caused not only increased frequency of discharges of a given unit but also a recruitment of additional units. Bronk and Stella also examined in detail the behavior of pressoreceptors at different static pressures in the vascularly isolated carotid sinus. Any one unit showed a particular threshold at which it began to fire, and increases of pressure beyond this threshold value accelerated the impulse discharge (Fig 2-42B) Pressure levels of 180 to 220 mm Hg were usually associated with maximal impulse frequency. Landgren (1952) considerably extended these studies, paying particular attention to the response of pressoreceptor fibers of different diameter De Castro (1951) showed that there were 700 myelinated fibers in the sinus nerve of the cat, 96 per cent of which were less than 5 μ in diameter. Only about 4 per cent of the pressoreceptor afferents were large (6 to 8 μ in diameter) Now, the spike height of the action potential of a single fiber is roughly proportional to the fiber diameter Moreover, it is much easier to isolate a large pressoreceptor fiber than a small one. It is possible, therefore, that undue attention has been paid to the behavior of large pressoreceptors, when one considers that the bulk of the reflexogenic activity of the sinus nerves is probably exerted by the overwhelmingly preponderant small pressoreceptor fibers However, Landgren (1952) found no striking difference in the behavior of the two "types" of pressoreceptors and this has been confirmed by Green (1954).

Studies on the conduction velocity of pressoreceptor afferents in the aortic nerve by Paintal (1953) have shown that it may lie in a range of 12 to 53 m/sec with a mean velocity of 33 m/sec. As an approximation, the conduction velocity in meters per second is five to six times that of the fiber diameter in microns. Hence 33 m/sec gives a value of about 5 to 6 μ for the diameter, and the higher velocities would correspond with the fibers in the 8- to 10-μ range

Carotid Sinus Reflexes. The carotid sinus can be isolated from the general circulation by tying the common carotid, external carotid, internal carotid, and occipital arteries. The technique is not simple, for obviously the integrity of the sinus nerve must be preserved during the placing of these ligatures Full details of the method of preparation are given by Heymans and Neil (1958). Once the sinus is "tight," a cannula connected to a pressure reservoir can be inserted into the common carotid artery and the isolated arterial segment, including the carotid bifurcation, can be subjected to any desired static pressure by merely raising the height of the reservoir. This technique, introduced by Moissejeff (1927), was extensively used by Koch (1931), with results which are famous. Two theoretical disadvantages are of relatively slight import—the pressure stimulus is nonpulsatile, and the nerve endings are not perfused The pressoreceptors, however, seem to require very little supply of nutrient, and a Moissejeff preparation will continue to yield sinus reflex responses for many hours.

Heymans (1929) introduced the technique of perfusion of the isolated carotid sinuses by means of a donor dog.

The common carotid arteries of the donor were anastomosed by Payr cannulas with the cephalic ends of the common carotid arteries of the recipient, and the external carotid arteries were anastomosed with the jugular veins of the donor. As all other branches of the carotid bifurcations of the recipient were tied, blood from the donor dog perfused the carotid sinuses of the recipient, finally to be returned via the external carotidojugular anastomoses to the donor animal A screw clip on the carotidojugular anastomoses allowed the maintenance of a suitable peripheral resistance in the carotid sinus segments A rise of pressure could be induced in the donor and, thereby, in the sinus region of the recipient by giving an intravenous injection of epinephrine.

Heymans and Bouckaert (1930) also used a Dale-Schuster pump in place of the donor animal to perfuse the carotid sinuses. De Burgh Daly (1955) has used a preparation similar to that of Moissejeff, on which he has superimposed pulsations delivered by a Dale-Schuster pump.

Lastly, the "blind-sac" preparation (Heymans et al., and others) may be mentioned, in which, after the internal and external and common carotid

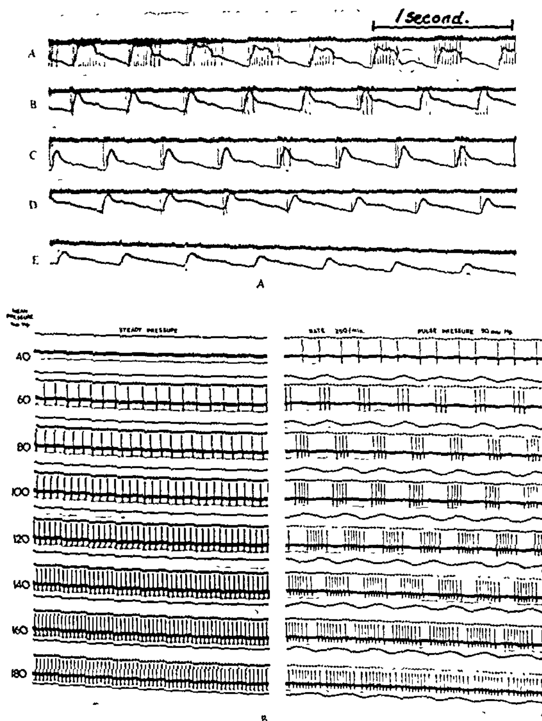


Fig 2-42 A Impulse activity in a single fiber of the left aortic nerve, and blood pressure recorded from the left ... A, 125, B, 80, C, ... activity in single ... segment Right, ... single pressureceptor of common carotid nerve during application of pulsations (250/min — *pulse pressure* — *50 mm Hg*) at different mean pressures Compare with figure on the left. (From Green.)

arteries and the occipital artery have been tied, a cannula carrying a balloon made of rubber filled with saline is slid into the common carotid artery, so that the balloon tip is in the vicinity of the sinus itself. The distention of the balloon, caused by increasing the saline pressure, produces deformation of the sinus and stimulation of the pressoreceptor endings.

With any of these techniques, the following reflex effects from the carotid sinus on the circulation may be shown:

1. *A rise of sinus pressure evokes reflex bradycardia and systemic hypotension* (Fig. 2-43A). Atropinization prevents the bradycardia but not the hypotension Hence, there are both a *cardiovagal reflex* and a *vasomotor reflex*. Bronk *showed that a rise of sinus pressure re*duced the impulse discharge in the sympathetic cardioaccelerator nerves and in the vasomotor nerves of the cervical sympathetic. Bacq et al showed that pressoreceptor vasomotor reflexes were completely abolished by complete excision of both paravertebral sympathetic chains. *The sympathetic vasoconstrictor outflow represents the sole efferent pathway of the sinoaortic reflexes* Parasympathetic vasodilator fibers do *not* participate in pressoreceptor vasomotor reflexes, and sympathetic *vasodilator nerves are not involved in pressoreceptor* vasomotor reflexes.

2. Whatever reflex responses occur in response to a rise of pressure in the isolated innervated carotid sinuses, they are quantitatively greater following section of the aortic nerves. This demonstrates the important "buffer" function of the pressoreceptor nerves in the intact circulation. Thus, *the aortic pressoreceptors are tonically active at ordinary systemic pressures.* An artificial stimulation of the pressoreceptors of the sinuses caused by a rise of perfusion pressure induces systemic hypotension, which in turn lessens the impulse *activity of the aortic nerves This lessened* firing from the aortic pressoreceptors causes a secondary "escape" of the vasomotor center, and the recrudescence of sympathetic *vasoconstrictor* impulses tends to offset the primary reflex effect of the raised sinus pressure. In natural conditions, however, changes of systemic pressure cause identical effects on all four of the sinoaortic zones.

3. By using the Moissejeff technique, the

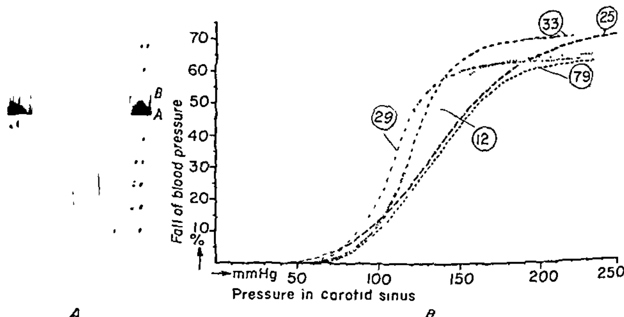


Fig. 2-43. A Dog. Right carotid sinus isolated by Moissejeff technique *A*, pressure in carotid sinus, *B*, systemic pressure (femoral artery); 1, increase of sinus pressure—induced reflex hypotension and bradycardia; 2, decrease of sinus pressure (*From C. Heymans, 1950.*) B "Blood pressure characteristic" curves of several dogs. Abscissa, pressure in carotid sinus; ordinate, *fall of* systemic blood pressure. (*From Koch, 1931.*)

isolated innervated sinus can be exposed progressively to pressures between zero and, say, 250 mm Hg Koch (1931) found that there was a threshold sinus pressure below which no reflex circulatory effects could be induced. This "threshold pressure" of the reflex response was of the order of 60 to 70 mm Hg. Increases of sinus pressure beyond this value caused greater reflex responses, and, by plotting the reflex response against the sinus pressure which caused it, he obtained the sigmoid *Blutdruckcharakteristik* curves (Fig. 2-43B). It can be seen that the greatest sensitivity of the systemic blood pressure to a change of sinus pressure occurs at a point on the curve in which the sinus and systemic pressures on the coordinates are of the value which is normal for the species. This important concept was confirmed and extended by Heymans et al (1931), using pulsatile pressures in the perfused carotid sinuses

The "threshold" concept of Koch allows an explanation of the reflex responses to carotid occlusion Thus, carotid occlusion causes reflex tachycardia and hypertension, *not* because any pressoreceptor of the sinus is stimulated by a drop of sinus pressure and thereby induces excitation of the cardioaccleratory and vasomotor centers, but because *the drop of sinus pressure removes a tonic discharge of inhibitory afferent impulses aroused by the normal level of the systemic pressure* Correspondingly, if the systemic pressure is unduly low prior to carotid occlusion, then the tonic activity of the inhibitory pressoreceptor afferents is likewise sparse and feeble, or even nonexistent, and subsequent carotid occlusion evokes no reflex response for the removal of nonexistent inhibition can cause no change in the situation

It is unwise to argue too closely from the results of carotid occlusion It is true that the major effects which follow carotid occlusion can be ascribed to *changes in the afferent impulse activity in the sinus nerves*, not to cerebral anemia as was thought by the earlier authors However, the drop in sinus pressure which is produced by carotid occlusion causes an excitation of the chemoreceptors of the carotid body, whose afferent fibers, traversing the sinus nerve, exert stimulatory effects on the vasomotor center.

It may be asked why the reflex systemic hypertension of carotid occlusion *may* be so marked as to justify its invariable use as a demonstration of sinus reflexes to students, when the sinus pressure recovers so rapidly through return of blood by anastomotic channels Common knowledge reveals that the reflex effects are well sustained, and the answer to the above query lies in the nature of the stimulus to pressoreceptor activity provided during the circumstances of carotid occlusion. The sinus pressure, albeit recovering to within say 20 per cent of its preocclusion value, is however only feebly pulsatile. Ead et al. (1952) *have shown that a sinus pressure which is pulsatile about a given mean is far more effective as an excitant of the pressoreceptors than a steady pressure of the same mean value* This finding, which is of considerable import in understanding the behavior of the pressoreceptors in the intact circulation, provides the explanation of the apparent paradox outlined above.

Common Carotid Pressoreceptor Reflexes. Green (1954) demonstrated that changes of static pressure in the common carotid artery segment containing the pressoreceptor endings evoke reflex effects of heart rate and blood pressure similar to those elicited *from* the carotid sinus

Right Subclavian Area. Neil (1956) perfused the right subclavian-carotid segment and obtained reflex hypotension on raising the perfusion pressure Similar results had been obtained by Nakayama (1953, 1954).

Aortic Area. Heymans and Ladon (1924, 1925) used a donor dog, A, to perfuse the head of a recipient dog, B.

The cephalic ends of the common carotid arteries of dog *B* were anastomosed to the cardiac ends of the common carotid arteries of dog *A* The jugular veins of the two dogs were similarly anastomosed, using Payr cannulas The head of dog *B* was completely separated from its trunk except for the vagi When a rise of pressure was induced in the trunk of *B* by any suitable means (e g, an injection of epinephrine), there ensued bradycardia (Fig. 2-44) This was reflex, being abolished by vagal section

Anrep and Starling (1925) perfused the head of a dog, *B*, by means of a heart-lung preparation made from another dog, *A* The trunk of *B* was supplied by its natural circulation

By clamping the lower thoracic aorta and thereby raising the cardioaortic pressure in the trunk of

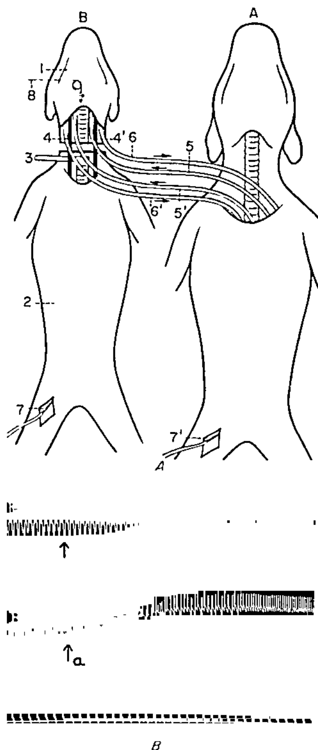


Fig. 2-44. A Arrangement for perfusion of the head of a dog, *B*, by donor dog, *A*. The head of dog *B* is attached to its trunk solely by the vagus nerves B Record from above downwards, respiratory movements of the larynx, *R*, of the isolated head of dog *B*, systemic pressure of the trunk of *B*. Time in 3-sec intervals At an injection of 0.1 mg epinephrine intravenously into trunk of *B*, systemic hypertension produces marked reflex bradycardia and apnea (*From C. Heymans*)

B, the blood pressure fell in the perfused head circuit. This was the first indisputable evidence of afferent vasoregulatory function of the cardioaortic vagal nerves. Section of the vagi abolished the response. Heymans and Bouckaert (1929) confirmed and extended these results.

EFFECTS OF SINOAORTIC PRESSORECEPTOR REFLEXES ON THE CARDIOVASCULAR SYSTEM

It has been proved that the sinoaortic pressoreceptor reflexes exert a tonic effect on the circulatory system Section of these nerves causes systemic hypertension and tachycardia The rise of blood pressure may be considerable, and the systemic pressure may temporarily exceed 300 mm Hg following acute sinoaortic denervation. It remains to consider the mechanisms whereby this hypertension is induced

It is generally recognized that the blood pressure is mainly determined by two factors—the cardiac output and the peripheral resistance.

The equation Blood pressure = cardiac output × peripheral resistance, is in some respects unfortunate, for it directs attention away from the capacity of the circulatory system. The capacity of the circulatory bed in man is roughly 5 to 6 liters, and perhaps 70 per cent of this is contained in the postarteriolar vessels, notably the veins and the venules. The arteries themselves have a marked resistance to stretch, as can be understood by considering the rise of pressure 40 mm Hg produced by a systolic output of 40 ml blood The volume elasticity coefficient is, therefore, 1 mm Hg/1 ml blood, or

$$\frac{1.36 \times 981}{1} \quad \frac{\text{dynes/cm}^2}{\text{ml}}$$

which is approximately 1,400 dynes/ml The circulatory system of a normal adult can however accommodate a blood volume change of 1,000 ml with a pressure change of 7 cm water and therefore has a volume elasticity coefficient of

$$E = \frac{7 \times 981}{1{,}000} = 7 \text{ dynes/ml}$$

Hence the arteries can accommodate only one-two hundredth of any volume added to the system, the remainder being accommodated in the low-pressure vessels (veins and intrathoracic vessels) Conversely, changes of capacity of the system are most likely effected by alterations of venomotor tone, whether induced neurogenically or by a myogenic property of the venous walls themselves It has not been

sufficiently understood that quite small changes produced by venoconstriction resulting in only 1 to 2 per cent of their capacity have profound effects on the venous return to the heart. Celander (1954) and Folkow (1955) have pointed out that as the veins contain 60 per cent or more of the total blood volume in a system in which the stroke volume of the pump is only 1 to 2 per cent, it can be calculated that a 1 to 2 per cent reduction of venous capacity will double the diastolic inflow to the heart from one heart beat to the next. A similar constriction of the arterioles would have only a negligible effect on the peripheral resistance.

The development of methods which measure flow is yielding evidence that we have been too prone in the past to describe changes in the circulation in terms of blood pressure and peripheral resistance. As Jarisch (1928) has said, "most organs require blood flow rather than blood pressure." It is probable that the *reflex venomotor effects exerted by the sinoaortic nerves are of paramount importance in allowing the adjustment of the capacity of the circulation and thereby influencing the venous return and the cardiac output.* The changes of peripheral resistance which occur with sinoaortic reflexes undoubtedly contribute to the autoadjustments of the circulations which these reflexes engender, but the danger in the past has lain in ascribing changes in the blood pressure only to changes of peripheral resistance.

The effects of sinoaortic reflexes on different aspects of cardiovascular activity may now be considered.

Cardiac Output. This measurement is not very satisfactory. The direct Fick method and the Hamilton dye method allow an assessment of the output only in terms of a minute and are ill suited to follow beat-to-beat variations in the stroke volume. The use of the cardiometer, while allowing the assessment of beat-to-beat variations, entails exposure of the heart and probably embarrasses cardiac performance. The introduction of flowmeters into the venae cavae or the pulmonary trunk likewise is attended by a host of alterations in the dynamics of the low-pressure systems in the thorax. It is for such reasons that the literature referring to the effects of sinoaortic reflexes on cardiac output is confused.

Early workers employed the direct Fick method. Chauber and Philippot found that carotid occlusion caused a marked rise in the cardiac output. Kenney et al. calculated that none of the animals used by them showed a rise of peripheral resistance of more than 4 per cent, indeed five of them showed a fall of (calculated) peripheral resistance. Kenney et al. could not, with one exception, find obvious changes of cardiac output in animals subjected to alterations of pressure in the isolated perfused carotid sinuses. Holt et al. used the Stewart technique for measuring cardiac output and reported that sinus nerve stimulation caused a fall of 7 per cent in the cardiac output (range −23 to 34 per cent). Leusen et al., using the Hamilton dye method, reported that a fall of sinus pressure caused an increase in the cardiac output. They stated that the rise of systemic blood pressure which occurred in these circumstances was largely achieved by this increase in cardiac output, rather than by an increase in the calculated peripheral resistance. Leusen et al. examined the *effect of a fall of pressure in the carotid sinuses* on the cardiac output of dogs before and after hemorrhage. Before hemorrhage, a sinus hypotension caused a rise of cardiac output of 33 per cent, an increase of blood pressure of 53 per cent, and an increase of total peripheral resistance of 12.5 per cent. After hemorrhage, a fall of sinus pressure increased the blood pressure by about 70 per cent, the cardiac output by 27 per cent, and the total peripheral resistance by 33 per cent. Hence, as the blood reservoirs are depleted by hemorrhage, the contribution which the constriction can make during sinus hypotension becomes of less importance and the relative contribution of arteriolar vasoconstriction becomes greater, according to these authors.

De Burgh Daly and Luck (personal communication) have studied beat-to-beat variations in the total flow recorded by a rotameter in the pulmonary trunk during changes of endosinus pressure. In 26 tests in 7 animals, a rise of carotid sinus pressure caused an average reduction of cardiac output of 14 per cent (range 8 to 46 per cent). A drop of cardiac output was seen even in animals which betrayed little evidence of reflex bradycardia. In some cases, the right atrial pressure fell, so that it could be argued that the reflex vasodilatation of the venous reservoirs resulted in a diminution of the venous return. However, in some cases, Daly and Luck found a rise of right atrial pressure which occurred on sinus hypertension attended by a reduction of cardiac output. This can mean only that the heart was failing to clear the blood "presented to it" by the venous return. Whereas reflex bradycardia might account for some of this failure, Daly and Luck showed that in these circumstances there was a profound reduction in the coronary flow which accompanied (and was probably due to) the reflex systemic hypotension. It was, therefore, likely that the diminished mechani-

cal efficiency of the ventricle was related to this reduction in coronary flow.

It is fair to point out that the experimental induction of reflex hypotension in the systemic circuit by raising the endosinus pressure brings about a chain of events which is abnormal. In the ordinary course of events, such pressoreceptor stimulation would be caused by a rise of systemic pressure. Hence the coronary flow in these circumstances would be greater than normal, and it is quite possible that the *marked reductions of coronary flow which Daly* has recorded in *his experimental conditions* do not occur, and consequently there is less chance of a fall in ventricular efficiency

The effect of cutting the vagoaortic nerves on cardiac output has been noted by Charlier and Philippot (1947), Charlier (1948), Kenney et al (1951), and Levy et al. (1954). No constant change has been described, and commonly no change occurs. As the vagoaortic *nerves contain numerous pressoreceptors from* the cardiopulmonary area besides those from the aortic arch, and as Aviado and Schmidt (1955) affirm that all pressoreceptors exert depressant actions on the cardiovascular system, this absence of change in the cardiac output is surprising. It suggests that there is still much to be learned about the mechanisms of control of the cardiac output

Heart Rate. Marey (1881) drew attention to the inverse relation between heart rate and the systemic blood pressure level Whereas François-Franck, followed by a score of others, believed that the systemic blood pressure level directly excited the cardiac vagal center, Hering (1927) disproved this and showed that the relationship resulted from the reflexogenic sinoaortic areas Hering, Heymans, and Koch developed the theme that *the resting cardiac vagal tone is reflexly engendered from the arterial pressoreceptor areas* Bronk et al (1936) showed that sinus hypertension caused an abolition of the activity of sympathetic impulses in the cardioacceleratory nerves. It is generally understood that tonic afferent impulse activity in the sinoaortic nerves is responsible for much of resting cardiac vagal tone; a rise of sinus pressure, therefore, increases vagal tone, whereas carotid occlusion induces reflex tachycardia. It is probable that resting vagal tone is not solely dependent on afferent activity in the arterial pressoreceptor fibers More recently, evidence of tonic afferent activity in *vagal fibers from the atria and ventricles and* from the pulmonary vessels has been obtained and, as will be seen below, these nerves induce reflex bradycardia.

Vasomotor Reflexes. KIDNEY. Stimulation of the aortic nerve causes an increase in the kidney volume because of vasodilatation. Renal vasodilatation was observed also in the perfused innervated kidney on stimulation of the aortic nerve and on traction of the common *carotid artery, respectively. Heymans (1929)* showed that common carotid occlusion evoked reflex vasoconstriction of the innervated kidney separately perfused by a donor dog On the other hand, the isolation of the kidney for perfusion or for organ plethysmography probably causes excessive renal vasoconstrictor tone (Smith, 1951), and the reflex responses thereby induced by sinoaortic stimulation may be misleadingly excessive. Rhoads et al. (1934) were *unable to demonstrate any resting* vasoconstrictor tone in the renal circulation by cocainizing the renal pedicle of a chronically exteriorized kidney Autoregulation of the renal circulation seems relatively independent of extrinsic nerves and is probably achieved by a physical mechanism (Pappenheimer and Kinter, 1956).

SPLEEN Heymans and coworkers (1929, 1931) showed that alteration of perfusion pressure *of the carotid sinus* causes reflex changes of caliber of the splenic vessels

A donor dog, *A*, was used to perfuse the carotid sinus of a dog, *B*, whose innervated spleen was in turn perfused by a second donor dog, *C* A rise of sinus pressure induced splenic vasodilatation, and conversely sinus hypertension caused splenic vasoconstriction. These findings were repeatedly confirmed

MESENTERIC BLOOD VESSELS Bayliss (1893), Bunch (1899), and Jarisch and Ludwig (1926) showed that an intestinal loop enclosed in an oncometer increases in volume during stimulation of the aortic nerve Tournade (1930) and Koch and Nordmann (1928) obtained corresponding effects by stimulation of the sinus nerve and converse effects on carotid occlusion. Heymans et al (1931) confirmed these findings and drew attention to the role of the mesenteric blood vessels as an important blood depot.

LIVER. Heymans et al (1930, 1931) and Gollwitzer-Meier and Schulte found that sinus hypertension induced an increase in the volume of the liver They considered that the liver acted as an important depot, whose capacity could be varied by sinoaortic reflexes.

LUNGS Lichtheim and several others stimulated the central end of the vagus and evoked a rise in pulmonary arterial pressure, but Schafer (1920), who stimulated the central end of the aortic nerve, reported a fall of pulmonary arterial pressure Tournade and Malméjac (1932) and Burstein (1946) obtained identical results on stimulation of the sinus nerve Daly and Schweitzer (1956), however, pointed out that unless the total pulmonary flow is measured, there can be no guarantee that the sinoaortic reflexes affect pulmonary vascular resistance at all. They proved that sinus hypertension always causes a *fall* of pulmonary arterial pressure and that carotid occlusion causes a rise of pulmonary arterial pressure. Daly and Luck have since shown that the pulmonary flow changes in the same direction as does the pulmonary arterial pressure, so that there is at present no reason to assume that the pulmonary vascular resistance is modified by sinoaortic pressoreceptor reflexes

CORONARY CIRCULATION Stella (1931) examined the effects of sinus reflexes on the coronary outflow measured by collecting coronary sinus blood via a Morawitz cannula He used a heart-lung-head preparation in which the left sinus was denervated and the right carotid sinus was isolated and perfused Sinus hypertension caused bradycardia and a great reduction in coronary flow By driving the heart electrically, he prevented the reflex bradycardia, whereupon sinus hypertension caused only a slight reduction of coronary flow

CEREBRAL CIRCULATION The cerebral circulation is not greatly influenced by vasomotor changes (Bouckaert and Jourdan, 1949; Schmidt, 1950) Thus, reflex changes of vasomotor activity, engendered by the sinoaortic reflexes, which affect the rest of the circulation, secure for the brain a satisfactory level of mean systemic blood pressure and flow

PERIPHERAL CIRCULATION Porter and Pratt (1908) and Tournade et al (1921) found that the vessels of a perfused innervated limb constricted when the systemic blood pressure fell, and vice versa. They attributed these vasomotor changes to direct effects of the blood pressure level on the vasomotor center itself. Heymans et al (1931) showed that the effects were reflexly induced via the sinoaortic nerves The vasoconstriction, reflexly induced by carotid occlusion, affected both the skin and the muscles (Crimson and Shen) Lindgren and Uvnas have extended these studies and have shown that the muscle vessels are under tonic sympathetic vasoconstrictor control which can be modified by the sinoaortic reflexes.

ADRENAL MEDULLARY SECRETION. Heymans made use of the ingenious suprarenal-jugular venous anastomosis of Tournade and Chabrol.

A donor dog, *A*, perfused the sinus of a recipient, *B* The right suprarenal vein of *B* was anastomosed with the jugular vein of a third dog, *C*, which was adrenalectomized. The volume of the spleen of C was measured oncometrically and reflected alterations of epinephrine secretion in dog B produced by changes in the carotid sinus pressure, induced in turn by raising the systemic pressure of dog A or by shutting off the sinus perfusion. A drop in sinus pressure in dog B caused a reflex secretion of epinephrine.

More recent studies by Holtz and Schumann agreed with those of Heymans, while Driver and Vogt could not confirm his findings. However, Brauner et al and Kaindl and von Euler obtained results similar to those of Heymans

VENOMOTOR TONE. The effects of sinoaortic reflexes on venomotor tone do not seem impressive because recording of venous pressure in an isolated innervated perfused venous segment is difficult They are, however, of very great importance Heymans et al showed that perfused innervated segments of the mesenteric veins constricted when the common carotid arteries were occluded and conversely dilated when the carotid sinus pressure was raised Similar observations were made using perfused innervated segments of colic vein by Fleisch (1930), and other confirmatory results were published by C[illegible]

[illegible] (or baroreceptor) *Nerve Endings.* Although Koch referred to the baroreceptor nerves as *Pressorezeptorische Nerven*, the true stimulus to the nerve ending is caused by *the displacement of the wall in which it lies* Hauss et al (1949) showed that the immobilization of the carotid sinus wall by means of a plaster of paris

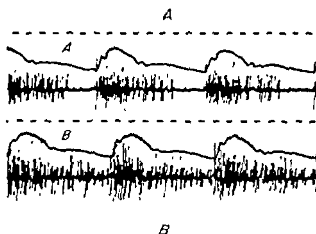


Fig. 2-45. A Dog anesthetized with morphine-chloralose Both vagoaortic nerves cut. Registration of blood pressure at femoral artery ↑1, clamping of carotid arteries, ↑2, declamping of carotid arteries; *between I and II*, infiltration of carotid sinus areas with 0.25 ml 1-norepinephrine (1/1,000); ↑3, clamping of carotid arteries, ↑4, declamping of carotid arteries, ↑5, section of carotid sinus nerves. *(From Heymans.)* B Action potentials from the carotid sinus nerve of the dog (sinus nerve cut) Blood pressure registered from the lingual artery Spontaneous respiration (air). Time, 25 cps. *A*, Control—mean blood pressure, 145 mm Hg; *B*, 4 min after local application of 0 25 ml 1-epinephrine HCL (1/1,000) —mean blood pressure, 145 mm Hg *(From Landgren, Neil, and Zotterman, 1952)*

cast abolished the sinus reflexes, normally evoked by a rise of endosinus pressure Palme (1943) noted that the local application of epinephrine to the sinus wall caused reflex hypotension but wrongly attributed this to stimulation of the nerve endings themselves by the drug Heymans and van den Heuvel-Heymans showed that this local action could be elicited by a large variety of drugs possessing only one common property—the ability to cause contraction of smooth muscle Systemic hypotension produced by the local application of such vasoconstrictor drugs was abolished by section of the sinus nerve and was, therefore, reflex (Fig. 2-45A). Landgren et al. confirmed these findings in electrophysiologic studies of the sinus afferent nerves (Fig. 2-45B). Heymans and coworkers showed that the contraction caused by epinephrine decreases the distensibility and increases the active muscular tension of the arterial wall in the isolated sinus. They ligated all branches of both carotid sinuses and opened the common carotid arteries proximal to the bifurcations. The sinuses were therefore empty and pulseless. Topical application of epinephrine caused reflex hypotension which was abolished by section of the sinus nerves Heymans and coworkers have shown that any vasoconstrictor drug causes an increase in the pressoreceptor discharge in these circumstances, which is the mechanism responsible for the reflex hypotension. It seems clear that the vasoconstrictor drug is *deforming* the pressoreceptors by causing contraction of the muscular elements of the wall. This deformation would seem to be the effective stimulus of the receptors, just as is the case with other types of mechanoreceptors. In normal circumstances, a receptor is stimulated by the deformation resulting from the expansion of the arterial wall caused by the rise of systolic pressure. If this expansion is prevented. the receptor is not stimulated Mechanical stimulation of the wall by *pressure over the sinus* causes reflex bradycardia in man, and this stimulation is more effective if the sinus wall has arteriosclerotic changes—indeed this mechanism is responsible for the *carotid sinus syndrome*, in which the slight pressure of a stiff collar may cause reflex syncope *Takayasu's syndrome* (chronic progressive obliterative brachiocephalic arteritis) may involve the carotid sinus leading to reflex syncope of this nature. Similarly, tugging on the carotid sinus during neck operations in animals or in man causes distortion and deformation of the receptors, which in turn discharge and produce reflex syncope.

Heymans and coworkers suggested that biologic changes of the vascular wall may be important in initiating the development of hypertension in man If the wall becomes less expansile, then the pressoreceptor mechanism is not stimulated to the same degree as would normally be the case McCubbin et al. (1956)

have shown that the pressoreceptor activity in dogs with chronic renal hypertension is much less than would be expected Lastly, it must be stressed that the pressoreceptors, like other mechanoreceptors, are responsive, not only to the *intensity* of the stimulus of deformation, but also to its *rate of application*. Thus, a pulsatile expansion of the arterial wall is much more effective in stimulating the nerve endings than a steadily maintained expansion, like that produced by a static pressure. Ead, Green, and Neil (1952) found that a pulsatile pressure in the sinus exerted a much greater reflex effect on the cardiovascular system than did a steady pressure of the same mean value.

Vascular Receptors Other Than Sinoaortic or Cardiopulmonary. MESENTERIC. Cammon and Bronk (1935) showed that pacinian corpuscles in the cat's mesentery were innervated by sensory fibers which coursed in the splanchnic nerves. These afferent fibers discharged with every pulse In the intact animal, the intravenous injection of 200 ml of Ringer's solution greatly increased the afferent discharge, conversely, hemorrhage resulted in cessation of discharge However, when a rise of systemic pressure was caused by vasoconstrictor drugs, e g, epinephrine, the discharge from the corpuscles ceased, whereas the intravenous *injection of amyl nitrite increased* the afferent firing They concluded that the total sensory discharge of the pacinian mesenteric receptors was determined by *the* blood volume, and hence their intravascular distention, rather than by the mean systemic blood pressure level

Heymans et al (1936) recorded the splenic volume changes in a recipient dog, B, whose spleen was perfused from a donor animal, A In dog B the sinovagal nerves *were cut* A sudden hemorrhage in dog *B* caused constriction of its isolated [illegible] by total sympathectomy or by destruction of the spinal cord Similar vascular responses were obtained in the perfused innervated hind limb by Heymans et al (1937), who proved that these reflexes originated from the mesenteric vessels Thus, if an innervated region of the gut with its attached mesentery was perfused by a donor dog, A, a rise of *perfusion* pressure in the mesentery of dog B resulted in reflex vasodilatation of the spleen It is likely that these mesenteric reflexes are concerned with the distribution of blood in the abdominal viscera These reflexes are of secondary importance to the sinoaortic reflexes

THORACIC AORTA RECEPTORS. Gruhzit and coworkers (1953) have proved that pressoreceptor reflexes may be initiated from the thoracic aorta. Tournade and Malméjac and Gayet et al. had previously shown that the intravenous injection of epinephrine still caused vasodilatation in an innervated, perfused limb even after sinovagal section Gruhzit et al. (1953) confirmed these findings and showed that the reflex was initiated by the stimulation of mechanoreceptors situated in the wall of the thoracic aorta; the afferent fibers are branches of thoracic sensory nerves These receptors responded to an increased pulse pressure but not to an increased mean blood pressure. The importance of these afferent mechanisms is not yet clear. There have been no electrophysiologic studies of these afferent fibers.

PERIPHERAL VASCULAR RECEPTORS. Edholm and McDowall (1936) showed that circulatory adjustments to posture could still be demonstrated in cats in which the sinovagal nerves were cut Gaskell and Burton (1953), and Yamada and Burton (1954) claimed that *venous receptors* exist in the walls of the small peripheral veins, which exert a vasoconstrictor effect on the arterioles supplying the limbs, via an axon reflex. The venous receptors are believed to be stimulated by *stretch* of the vessel walls Haddy and Gilbert (1956), using anesthetized dogs, obtained evidence that venous receptors, excited by stretch of the venous walls of the limbs, may cause a reflex vasomotor constriction of the small arterioles, mediated by the sympathetic nerves and consequently abolished by sympathectomy. In the absence of this reflex, the flow through a limb would inevitably increase as it was lowered below heart level. Reflex peripheral vasoconstriction would thus tend to prevent pooling of blood

It is interesting that heart failure is often associated with intense peripheral vasoconstriction—which may even lead to *gangrene of the* fingers and nose This may be abolished by sympatholytic agents or venesection. It is possible that reflexes, such as that described by Haddy and Gilbert (1956), are responsible for the peripheral vasoconstriction seen in heart failure.

CHEMORECEPTORS AND CHEMORECEPTOR VASOMOTOR REFLEXES

Anatomy

Chemoreceptor reflexogenic areas are found in the carotid body and the aortic bodies (Fig. 2-41).

The Carotid Body. The carotid body lies at the origin of the occipital artery or the ascending pharyngeal artery, immediately headward to the carotid bifurcation. De Castro (1926, 1928) was the first to recognize the extraordinarily rich sensory innervation of the tissue by the sinus nerve. He showed that the organ was composed of epithelioid cells which were in close contact with numerous sinusoidal blood vessels (*una complejisima red de vasos sinusoidales con infinidad de anastomoses*). The epithelioid cells present one aspect directed towards the sinusoids (*pôle sanguin*), and another which is supplied by the sensory nerves (*pôle nerveux*). De Castro concluded that the carotid body might sample qualitative changes in the blood composition. Goormaghtigh and Pannier (1939) drew attention to the arteriovenous anastomoses which exist in the carotid and aortic bodies, and de Castro (1940) confirmed them.

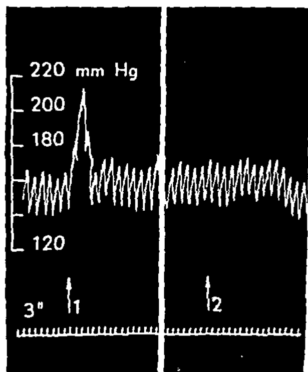


Fig. 2-46. Dog, chloralose anesthesia. Arterial blood pressure recorded from femoral artery 1 Injection into normal common carotid artery of 0 5 ml buffered sodium bicarbonate (3 per cent solution). The internal and external carotid arteries are ligated, and carotid blood flow is directed to the carotid body. The bicarbonate solution produces reflex hypertension by stimulating the carotid body. 2 Injection of 0 5 ml buffered sodium bicarbonate (3 per cent solution) into common carotid artery of the opposite side. On this side, the carotid body is excluded by a ligature from the carotid circulation and the external carotid artery is tied. The carotid blood is directed through and towards the medullary vasomotor center via the internal carotid artery No hypertension is produced by injection. (*From Heymans, Bouckaert, von Euler, and Dautrebande, 1932*)

The carotid body is supplied by arterial blood vessels from the occipital artery or ascending pharyngeal artery, and its venous blood drains into the internal jugular vein. The blood flow through the tissue is enormous, being equivalent to 2,000 ml/100 Gm carotid body tissue per minute. This tremendous blood flow (thirty times that for the brain, weight for weight) was not appreciated until the measurements were made by Daly et al (1954) As the organ weighs some 2 mg in the cat, the total flow is only 40 mm^3/min; this seems trivial until expressed in terms of flow per 100 Gm/min. The oxygen usage of the organ is 9 ml/min/100 Gm carotid body tissue, which is three times that of brain tissue Heymans and Neil (1958) give full details of the development, histology, and comparative anatomy of this structure

Aortic Bodies. Epithelioid tissue, similar in structure to that of the carotid body, occurs in various groups scattered on the anterior surface of the aortic arch, in the concavity of the aortic arch, and at the roots of the left and right subclavian arteries. These cell groups have as their sensory innervation the aortic nerves.

Chemoreceptor Reflexes

The Heymans (1927) discovered the aortic chemoreflexes by a technique similar to that outlined for the demonstration of the aortic pressoreceptor reflexes.

Heymans et al (1931) proved that the carotid body was the site of chemoreflexes If blood of high P_{CO_2} or low P_{O_2} was perfused through the innervated carotid body, hyperpnea resulted Animals breathing low oxygen mixtures developed hyperpnea, if the sinovagal nerves were cut, the inhalation of low oxygen mixtures caused respiratory depression. The sinoaortic chemoreflexes were thus shown to be

vital for hypoxic hyperpnea. Heymans et al (1932) studied the chemoreceptor vasomotor reflexes. They found that *chemoreceptor excitation caused reflex hypertension* (Fig 2-46) *and bradycardia* They showed that nicotine, lobeline, and cyanide were important stimulants of the chemoreceptors, and Comroe (1939) used these substances for investigating the aortic chemoreflexes in the intact animal

By pushing a catheter in a retrograde direction from the common carotid artery into the aorta, the tip of the catheter could be arranged to lie in the ascending part of the aortic arch The injection of small doses of cyanide caused reflex hyperpnea and hypertension, which was abolished by vagal section His results were confirmed and extended by Gernandt (1946) and Neil et al (1949)

Electrophysiology of the Chemoreceptor Nerves. Heymans and Rijlant (1933), Bogue and Stella (1935), and others recorded impulse activity from the sinus nerve, which was increased by hypoxia, hypercapnia, asphyxia, or acidosis The impulse activity of the sinus nerve is of course complicated by the presence of the sinus pressoreceptor afferents By splitting the nerve fiber, preparations can be obtained of either pressoreceptor or chemoreceptor type The impulse activities of these two kinds of nerve fibers are different (Fig 2-47A, B, Table 2-3)

Von Euler et al (1939), Gernandt (1946), Landgren and Neil (1951), and Duke at al (1953) have expanded these early studies It can be stated that some sparse impulse activity occurs in the chemoreceptor fibers in anesthetized animals breathing room air or oxygen This is aroused by the arterial P_{CO_2} and, in animals breathing room air, by the arterial P_{O_2} (Bartels and Witzleb, 1956) It is probable that this chemoreceptor impulse activity exerts little, if any, influence on the circulation in normal conditions

Chemoreceptor Response to Hypoxia. The chemoreceptors are excited by hypoxia, of the four types of hypoxia (hypoxic, anemic, stagnant, and histotoxic), all stimulate the chemoreceptors except anemic hypoxia Comroe and Schmidt (1938) *first showed that the chemoreceptor reflexes were not excited by a fall of oxygen content in the arterial blood, provided that the oxygen tension of the blood was maintained, and concluded that the oxygen demands*

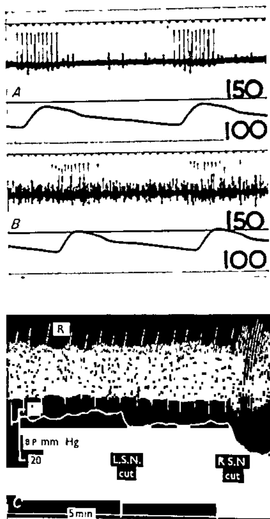


Fig 2-47 Cat, thiopentone anesthesia Right sinus nerve cut centrally and a thin slip laid on saline wick electrodes Action potentials recorded on an oscillograph via a resistance-capacity coupled amplifier Blood pressure recorded from the femoral artery by condenser manometer Records from above downwards, time trace 50 cps, electroneurogram of thin slip of sinus nerve, blood pressure Calibration lines of pressures of 150 and 100 mm Hg are shown A Cat breathing air spontaneously. B Cat breathing 10 per cent oxygen in nitrogen spontaneously Note increase in chemoreceptor activity during hypoxia. (*From Heymans and Neil, 1958*) C Cat, chloralose anesthesia, both vagi cut, previously bled to reduce systemic pressure to 65 mm Hg Records from above downwards, respiration, blood pressure, signal, and time in 5-sec intervals Note the effects of successive section of the right and left sinus nerves. Fall of blood pressure occurs because of interruption of chemoreceptor afferents (*From Kenney and Neil, 1951*)

TABLE 2-3. IMPULSE ACTIVITIES OF PRESSORECEPTORS AND CHEMORECEPTORS

Condition	*Pressoreceptor*	*Chemoreceptor*
Relation to pulse	Fires with each pulse	No relation
Carotid occlusion	Abolished or lessened	Increase
Epinephrine hypertension	Increase	Decrease
Hypoxia	No effect	Increase
Asphyxia	No effect	Increase
Hypercapnia	No effect	Increase
Acidemia	No effect	Increase
Lobeline	Little effect	Enormous increase
Hemorrhagic hypotension	Abolished or lessened	Enormous increase

of the carotid body were modest, being satisfied by the small amount of dissolved oxygen in the arterial blood at normal arterial P_{O_2}. Duke, Green, and Neil substantiated these findings in a direct examination of chemoreceptor impulse activity. No impulse discharge was aroused, even when the arterial blood contained 80 per cent carboxyhemoglobin, providing that the arterial P_{O_2} was maintained Hence, carboxyhemoglobinemia or methemoglobinemia does not induce chemoreceptor reflexes.

The explanation given by Comroe and Schmidt must be modified in the light of the findings of de Burgh Daly et al (1953) of the enormous blood flow through the chemoreceptors. The chemoreceptors have a very high rate of metabolism, but the blood flow is so high that a fall in oxygen *content* of the blood does not seriously impair the oxygen supplies of the tissue Hemorrhage, or any state of hypotension, by reducing the mean systemic pressure, gravely reduces the blood flow through the carotid body, and correspondingly allows an accumulation of metabolites, which excite the nerve endings In addition, hemorrhagic hypotension is attended by increased sympathetic vasomotor activity in postganglionic fibers supplying the afferent vessels of the carotid body, and thereby further reduces the carotid body blood flow.

In summary, *stimulation of the chemoreceptors by hypoxia, asphyxia, hypercapnia, or acidosis causes reflex vasomotor stimulation and possibly bradycardia* The contribution of the chemoreceptors to the control of the circulation at rest is probably negligible

Hemorrhage. The chemoreceptor reflexes are extremely active in hemorrhagic hypotension (Landgren and Neil, 1951). McDowall (1924) noted that vagal section in bled animals caused a fall in blood pressure—the McDowall effect. In normal animals, vagal section causes a rise of blood pressure because of the interruption of tonic pressoreceptor inhibitory impulses In hemorrhagic hypotension, the pressoreceptors are minimally active, and a drop of pressure on vagal section reveals that some fibers which were maintaining the blood pressure must have been interrupted Comroe (1939) suggested that the chemoreceptor fibers might be maintaining vasomotor center activity after hemorrhage, and this suggestion was proved by Kenney and Neil (1950). They found that temporary blockade of the vagi (by cooling) caused a fall of blood pressure in bled animals; selective elimination of the aortic chemoreceptors was then achieved by the local injection of acetic acid (Gernandt, 1946); following chemoreceptor inactivation, vagal blockade no longer caused a fall of blood pressure Kenney and Neil pointed out that the complex fiber components of the vagi made it unwise to argue too closely, but they considerably strengthened their case by showing that sinus nerve section caused a fall of blood pressure in bled animals (Fig 2-47C). As the sinus nerves contain only presso- and chemoreceptor fibers, and as the section of pressoreceptor fibers could not possibly cause a fall of blood pressure, this response must have been due to the interruption of chemoreceptor impulses

Mayer Waves. It is common knowledge that the blood pressure in animals or patients with enfeebled circulation may show a rhythmic variation other than that occasioned by the effects of respiration These waves, usually de-

scribed in the literature quite wrongly as *Traube-Hering waves*, were initially noted by Sigmund Mayer (1876) and should be designated as *Mayer waves* Their periodicity is much slower than that due to respiration. If the common carotid arteries are occluded in an animal which shows Mayer waves at rest after bleeding, the waves enormously increase in amplitude but are not affected in their periodicity Andersson et al (1951) analyzed this phenomenon and showed that *the Mayer waves were initiated by the chemoreceptors.* Thus, as the blood pressure reaches low levels, chemoreceptor excitation occurs and reflex vasomotor stimulation ensues which raises the blood pressure The increased blood pressure level induces pressoreceptor activity and reduces chemoreceptor stimulation, whereupon the blood pressure falls to a low level Then, the cycle repeats itself Mayer waves can be abolished by inactivation of the chemoreceptors through local injection of acetic acid

Heart Rate. Heymans and coworkers, Bernthal, and Comroe and Schmidt showed that the local injection of drugs such as nicotine, sodium sulfide, sodium cyanide, etc , which cause powerful chemoreceptor excitation is associated with reflex bradycardia Bernthal et al (1951) reinvestigated the reflex effects on the heart rate of perfusing the carotid body with sodium cyanide solutions or with solutions of low P_{O_2}. The dogs were ventilated artificially with room air, and the systemic blood pressure was stabilized *Bradycardia occurred as a reflex response to hypoxia or cyanide* Neil and Landgren and Neil pointed out that Bernthal's results, though interesting in themselves, throw no light on the heart rate responses to chemoreceptor stimulation during systemic hypoxia. The effect of chemoreceptor impulse activity may be modified when the medullary centers are themselves hypoxic Neil exposed cats to systemic hypoxia, having arranged the carotid body circulation so that it can be supplied by systemic blood or by an oxygenated perfusion fluid When hypoxic tachycardia and hypertension had been induced, the carotid body blood supply was replaced by a supply of oxygenated fluid The hyperpnea and hypertension subsided, but there were no changes of heart rate On reestablishing the flow of hypoxic blood through the carotid body, there were again no immediate changes of heart rate, although respiration and blood pressure resumed their previous levels. It would seem that *hypoxic tachycardia* has its origin elsewhere than from a reflex initiated by the chemoreceptors On the other hand, there was little evidence that the chemoreceptors, subjected to physiologic stimuli, evoked reflex bradycardia during hypoxia in the cat.

Green and Neil have found that lobeline, nicotine, sodium sulfide, and sodium cyanide, when injected into the carotid artery, cause pressoreceptor excitation as well as exciting chemoreceptors Hence the drug effects may merely display a pressoreceptor reflex effect.

Daly and Daly (1957) have shown that the perfusion of mixed venous blood, pumped from the right heart through the carotid body, causes reflex bradycardia in the dog breathing room air It will be interesting to discover whether the response can be obtained during systemic hypoxia

CARDIOPULMONARY REFLEXES

Anatomy

Detailed accounts of the innervation of the cardiopulmonary area have been presented by Tigerstedt (1921), Nonídez (1937–1943), Dawes and Widdicombe (1953), and Mizeres (1955).

Much of the earlier work was done by ordinary anatomic dissection using methylene blue staining. The nerves innervating the cardiopulmonary area are both afferent and efferent, and sympathetic fibers often join vagal branches and vice versa Therefore, it is only with the development of silver-staining techniques (Nonídez), in which nerve branches are examined histologically (following chronic stellectomy or supranodose or infranodose vagotomy), that much headway has been made in identifying the nature of nerve fibers in a given macroscopic branch To this technique has been added that of the *electroneurogram,* which alone can give indisputable evidence of the presence of afferent or efferent fibers

Conventionally, one describes *three cardiosympathetic nerves on each side* arising from the superior, middle, and inferior cervical ganglia and named accordingly (Kuntz, 1945) Their preganglionic fibers arise from T_1 to T_5 The cardiovagal nerves are described by Nonídez Important data have been collected as to the fiber components of the cardiovagal nerves by Daly and Evans (1953) and Agostoni

et al. (1957). The cardiac vagal branches in the cat contain in all about 3,000 fibers Only 500 fibers, mostly nonmyelinated, disappear after supranodose vagotomy and are therefore efferent; the remainder, which are afferent, are mostly nonmyelinated, but there are some 700 myelinated fibers in the 1- to 12-μ range. The pulmonary vessels receive a rich sympathetic innervation (Karsner, 1911; Larsell, 1921), which is predominantly *vasoconstrictor* (de Burgh Daly and his school, 1933–1952).

Electroneurography of the Cardiopulmonary Afferent Fibers

Although von Bezold and Hirt (1867) described the cardiac reflex effect of veratrine, it was not until Jarisch and his colleagues (1938–1949) revived the concept of "proprioceptive"

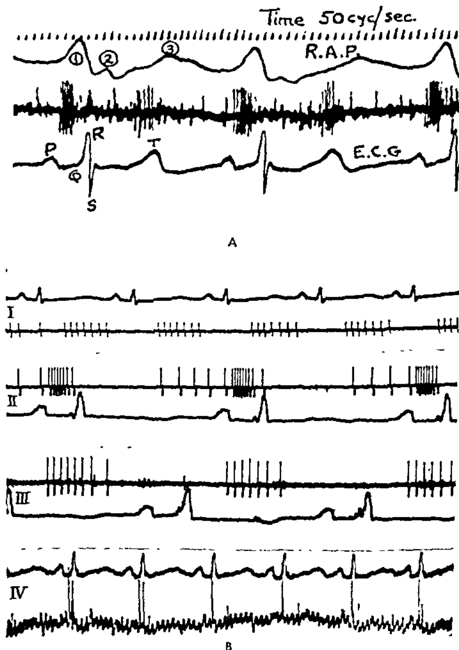


Fig. 2-48 A Records taken of impulse activity of a thin slip of the cardiac vagus (central end) Multifiber preparation Records from above downwards, time—50 cps, right atrial pressure, electroneurogram, and ECG (From Neil and Zotterman, 1950) B I, II, III, and IV show ECG and electroneurogram of four separate preparations of cardiac vagal afferents I, "B" type atrial receptor (right atrium), II, "A" type atrial receptor (right atrium); III, arterial pressoreceptor from the aortic arch, IV, right ventricular receptor. (From Heymans and Neil, 1958.)

receptors in the heart that much interest was devoted to the cardiac afferent fibers. The following afferent fibers have been described:

Atrial Receptors. These are found in both left and right atria and are of two types, "A" and "B." "A" receptors discharge in atrial systole in the P-R interval and perhaps again during the venous filling wave of each cardiac cycle. Their nerve fibers have a mean conduction velocity of 20 m/sec. "B" receptors discharge only during the venous filling wave, and their activity is increased by lowering the intrathoracic pressure and decreased by positive-pressure inflation of the lungs. Their mean conduction velocity is 13 m/sec (Paintal, 1953) (Fig. 2-48).

Ventricular Receptors. These evince an early systolic outburst of the impulses within 20 to 60 msec of the Q wave of the ECG. They discharge then in the phase of isometric contraction of the ventricles (Fig. 2-48).

Pulmonary Arterial Pressoreceptors (Swan and Whitteridge, 1956). These discharge 50 to 65 msec after the Q wave, cease firing when the pulmonary artery is occluded, and increase their firing when the pulmonary capillaries are embolized with starch granules.

Pulmonary Deflation Receptors. These receptors, situated in the vicinity of the alveoli (Paintal, 1955), are normally quiescent and can be excited by suction of air from the lungs. Their activity is notably increased by injection of phenyl diguanide and is also increased by multiple pulmonary embolization. Their fiber conduction velocity is 6 m/sec, and the cervical vagus must be cooled below 3 to 4°C before these fibers cease to conduct. They are, therefore, small afferent fibers.

Reflexes from the Heart and Lung Vessels

The classical technique of vascular isolation and perfusion is difficult to apply in the investigation of the cardiopulmonary reflexes. Some results of such techniques are available. In addition, there is considerable evidence of the reflex functions of the cardiopulmonary afferents from the artificial stimulation of the receptors by drugs and from the results of multiple capillary pulmonary embolization.

Reflexes from the Right Side of the Heart. Aviado et al. (1951) isolated the blood flow in the right heart by collecting the blood from both venae cavae and pumping it into the right atrium, then collecting it via a cannula in the pulmonary artery, and leading it to a pump, which finally returned it after oxygenation to the left atrium. A rise of perfusion pressure in the right heart caused reflex hypotension and bradycardia (abolished by vagotomy). The reflex originated from atrial vagal receptors.

Reflexes from the Pulmonary Vessels. PERFUSION STUDIES. Churchill and Cope (1929), Schwiegk (1935), and Schweitzer (1936) obtained small but definite reflex bradycardia and hypotension by raising the static pressure in an isolated but innervated lung. The responses were abolished by vagotomy. Aviado et al. (1951), by a specialized perfusion method, obtained vagal reflex bradycardia by raising the pulmonary arterial pressure. Daly et al. (1937) showed that a rise of pulmonary venous pressure caused vagal reflex systemic hypotension. Aviado et al. (1951) induced reflex systemic hypotension and tachypnea by raising the perfusion pressure in the pulmonary veins.

THE PULMONARY DEPRESSOR CHEMOREFLEX (Dawes and Comroe, 1954). The name of this reflex is unfortunate; the reflex is probably initiated from the pulmonary deflation receptors but was first described as a response to the injection of phenyl diguanide and various amidines. The intravenous injection of 50 to 100 µg of phenyl diguanide induces bradycardia, hypotension, and apnea. The response is still present after vagal cooling to 3°C and is, therefore, mediated by small vagal fibers. Paintal has proved that the amidines stimulate the pulmonary deflation receptors and that these represent the sensory arm of the "pulmonary depressor chemoreflex." Likewise serotonin, nicotine, and multiple embolization of the pulmonary capillaries by starch, all stimulate both the pulmonary deflation receptors and evoke the "*pulmonary depressor chemoreflex*." It is possible that these receptors are stimulated by serotonin released from platelets following natural embolization in the pulmonary vessels, thus being responsible for some of the reflex effects of multiple embolization.

INITIATION OF PULMONARY VASOCONSTRICTION BY PULMONARY VASCULAR RECEPTORS. Clinical evidence of pulmonary vasoconstriction of reflex origin derives from the work of Dexter and his colleagues (1948–1952). Dexter found that the "pulmonary capillary pressure" (P.C.P.), measured by wedging a cathe-

et al. (1957). The cardiac vagal branches in the cat contain in all about 3,000 fibers Only 500 fibers, mostly nonmyelinated, disappear after supranodose vagotomy and are therefore efferent, the remainder, which are afferent, are mostly nonmyelinated, but there are some 700 myelinated fibers in the 1- to 12-μ range. The pulmonary vessels receive a rich sympathetic innervation (Karsner, 1911; Larsell, 1921), which is predominantly *vasoconstrictor* (de Burgh Daly and his school, 1933–1952).

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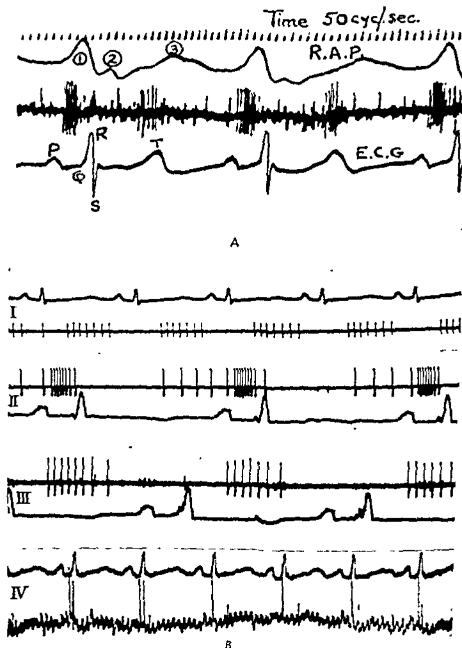


Fig. 2-48. A. Records taken of impulse activity of a thin slip of the cardiac vagus (central end) Multifiber preparation Records from above downwards, time—50 cps, right atrial pressure, electroneurogram, and ECG. (*From Neil and Zotterman, 1950*) B I, II, III, and IV show ECG and electroneurogram of four separate preparations of cardiac vagal afferents. I, "B" type atrial receptor (right atrium); II, "A" type atrial receptor (right atrium), III, arterial pressoreceptor from the aortic arch; IV, right ventricular receptor. (*From Heymans and Neil, 1958*)

announced by Nonídez (1937). Aviado and Schmidt (1955) have concluded that all the cardiopulmonary pressoreceptor afferent nerves exert depressant actions on both heart rate and blood pressure Hence, a marked increase in venous return which causes engorgement of both the right heart and pulmonary bed is likely to evoke reflex bradycardia engendered by these receptors Nevertheless, tachycardia occurs, which, if it is admitted to be reflex, must presumably be a powerful reflex. Knoll (1881), Hering (1924), and Anrep et al (1936) have shown that feeble faradic stimulation of the central end of the pulmonary vagal fibers induces marked tachycardia (feeble stimulation is imperative, for stronger stimuli evoke reflex bradycardia). These facts suggest (1) that the reflex is mediated by large (easily excitable) afferent fibers; (2) that the Bainbridge reflex may arise from vagal afferents in the pulmonary bed or the lung parenchyma Obviously more work is needed here

ter tip in a small artery of the lung (2 to 3 mm in diameter), was raised in patients with mitral stenosis. The calculated pulmonary arterial resistance (P.A.R.) was sensibly normal, however, unless the P.C.P. approached 20 to 25 mm Hg—whereupon the P.A.R. markedly increased. This increase of P A R was ascribed to active vasoconstriction reflexly engendered from the pulmonary vessels and serving to protect the pulmonary capillaries from a high hydrostatic pressure with the consequent danger of pulmonary edema. Whereas some of the rise in P.A.R. in chronic mitral stenosis is due to organic medial hypertrophy of the small pulmonary arteries, Dexter (1952) has reported a dramatic fall of P.A.R. following mitral valvotomy in such patients. There is as yet no evidence as to the site of these hypothetic receptors.

Reflexes from the Left Heart. Daly and Verney (1927) and Aviado et al. (1951) have shown that a rise of pressure in the left atrium and left ventricle causes vagal reflex bradycardia and vasodilatation As Aviado and Schmidt (1955) point out, the quantitative responses are rather feeble, probably because of the technical difficulties entailing wide operative exposure and deterioration of the preparation

The Bezold-Jarisch Reflex. Veratrine (or its constituents) causes reflex vagal bradycardia and hypotension, because of the stimulation of ventricular receptors and perhaps atrial receptors (Paintal) This proof of the view held by Jarisch (1938–1949) completes a long period of investigation and terminates a considerable amount of dispute Dawes (1947) was the first to show that veratrine, injected directly into the coronary artery, evoked the Bezold effect in doses one-twentieth of those required to elicit the reflex when given intravenously The term "coronary chemoreflex" was coined by Dawes and Comroe (1954) to describe this reflex response to veratrine. The name is misleading; the Bezold reflex is an artificial stimulation of ventricular *mechanoreceptors* by a drug The normal function of these receptors would seem to be a proprioceptive one (as envisaged by Cyon and Ludwig for the depressor nerve endings and by Jarisch in the case of the cardiac receptors themselves)

The Role of Left Atrial Receptors in the Reflex Control of Blood Volume. Henry and his colleagues have suggested that the left atrial vagal afferents form the sensory arm of a reflex which controls blood volume. Negative pressure caused through artificial ventilation is followed by diuresis, if the vagi are cut, this response no longer occurs. Henry has shown recently that a rise of pressure in or a distention of the left atrium is the initiating stimulus of the diuretic response Distention of the left atrium evokes discharge of the left atrial receptor fibers He concluded that these sensory areas in the low-pressure part of the cardiovascular system might thus reflexly alleviate circulatory engorgement, such as occurs in hydremic plethora; conversely, the reduction of tonic atrial receptor activity following hemorrhage might assist in the maintenance of blood volume by reducing fluid loss in the urine

The Bainbridge Reflex. It may seem puzzling that this well-known reflex is considered last However, there is as yet no evidence of the receptor mechanisms responsible for the reflex cardiac acceleration caused by increased venous return, first described by Bainbridge (1915). Some deny even that there is a cardiac acceleration following a sudden increase in the venous return (Jarisch and Zotterman, 1948, Wiggers, 1949). However, the well-documented papers of Anrep and Segall (1926), Ballin and Katz (1941), Bouckaert and Pannier (1942), and Coleridge and Linden (1955) show that the response occurs, particularly if the preinfusion heart rate is slow because of a good background of resting vagal tone Nevertheless, it is not essential that the response be a reflex one. Thus Ludwig and Luchsinger (1881) and Hobbs et al. (1926) have shown that an increase in the diastolic tension of the cardiac fibers renders the frog heart less responsive to vagal activity Tutso (1937) and Blinks (1956) have evoked tachycardia in the isolated perfused mammalian heart by increasing its perfusion pressure

Bainbridge claimed that the reflex was initiated by the stimulation of vagal receptors on the venous side of the heart, which in turn induced a reduction of vagal efferent activity with a concomitant stimulation of sympathetic cardioacceleratory activity Ballin and Katz (1941) and Aviado et al (1951) could not evoke tachycardia by distending the right heart or by raising its perfusion pressure, so it would seem unlikely that the atrial caval receptors represent the sensory arm of the reflex as was

announced by Nonidez (1937). Aviado and Schmidt (1955) have concluded that all the cardiopulmonary pressoreceptor afferent nerves exert *depressant actions* on both heart rate and blood pressure. Hence, a marked increase in venous return which causes engorgement of both the right heart and pulmonary bed is likely to evoke reflex bradycardia engendered by these receptors. Nevertheless, tachycardia occurs, which, if it is admitted to be reflex, must presumably be a powerful reflex. Knoll (1881), Hering (1924), and Anrep et al. (1936) have *shown* that feeble faradic stimulation of the central end of the pulmonary vagal fibers induces marked tachycardia (feeble stimulation is imperative, for stronger stimuli evoke reflex bradycardia). These facts suggest (1) that the reflex is mediated by large (easily excitable) afferent fibers; (2) that the Bainbridge reflex may arise from vagal afferents in the pulmonary bed or the lung parenchyma. Obviously more work is needed here.

I

Arterial pressure and its control

H. S. MAYERSON

In 1733, the Reverend Stephen Hales of Teddington, England, made a pioneer experiment to observe and record arterial pressure He wrote:

> "I caused a mare to be tied down alive on her back; she was 14 hands high and about 14 years of age, had a fistula on her withers, was neither very lean or very lusty having laid open the left crural artery about 3 inches from her belly, I inserted into it a brass pipe whose bore was 1/6 of an inch in diameter, and to that, by means of another brass pipe which was fitly adapted to it, I fixed a glass tube, of nearly the same diameter, which was 9 feet in length then untying the ligature on the artery, the blood rose in the tube 8 feet 3 inches perpendicular above the level of the left ventricle of the heart. but it did not attain to its full height at once, it rushed up about half way in an instant, and afterwards gradually at each pulse 12, 8, 6, 4, 2 and sometimes 1 inch when it was at its full height, it would rise and fall at and after each pulse 2, 3, or 4 inches, and sometimes it would fall 12 or 14 inches, and have there for a time the same vibrations up and down, at and after each pulse, as it had, when it was at its full height, to which it would rise again, after forty or fifty pulses"

This is the first recorded observation of mean blood pressure.

Obviously, the method employed by Hales has great disadvantages in being technically inconvenient and inaccurate because of the increase in the capacity of the circulatory system incident to using a long section of tubing Poiseuille obviated this difficulty when he introduced the mercury manometer (1828), and Ludwig (1847) placed a float on the mercury column and introduced the method of continuous, permanent recording of blood pressure on a kymograph, familiar to every student who has taken physiology. This is still a most satisfactory method for recording mean arterial pressure. More modern adaptations of the direct method are discussed by Green (1950), Rushmer (1955), and Fry (1957).

The *mean arterial pressure* is the average of all the successive pressures during each portion of the pulse pressure curve It is usually slightly less than the average of systolic and diastolic pressures, because the average pressure throughout the cardiac cycle is closer to the diastolic than the systolic level In the average young adult who has a normal systolic pressure of 120 mm Hg and a diastolic pressure of 80 mm Hg, *the mean arterial pressure is approximately 96 mm Hg.* Mean arterial pressure is a function of the product of cardiac output and peripheral resistance, and any factors which influence these will modify the level of mean arterial pressure. Thus, changes in heart rate, stroke output, or both, will result in corresponding changes in mean blood pressure if the peripheral resistance is unchanged Likewise, changes in arteriolar tone, the chief determinant of peripheral resistance, will modify the level of mean arterial pressure unless or until the cardiac output is inversely readjusted

Although the determination of mean blood pressure yields important data concerning circulatory mechanisms and is invaluable in experimental work, cannulization of arteries is usually impractical in clinical medicine, and the method has therefore found limited use in the

study and examination of patients.[1] The indirect measurement of blood pressure by means of a cuff was introduced by Riva-Rocci (1896), who used a 5-mm cuff Von Recklinghausen (1901) suggested that more accurate results could be obtained by the use of a 13-mm cuff, and this has become the standard width for the auscultatory method of measurement of blood pressure, except in children The sphygmomanometer method provides for the determination of systolic and diastolic pressures and the calculation of pulse pressure as the difference between the two pressure values The method is subject to errors in procedure and in use of faulty apparatus Even where the method is correctly used, direct registration of pressures by calibrated intraarterial manometers has shown (1) that during quiet breathing and slight sinus arrhythmia, systolic and diastolic pressures vary from beat to beat by several millimeters of mercury and that these differences are greatly intensified during states of arrhythmia and deep breathing, (2) that auscultatory systolic readings from the brachial artery average 3 or 4 mm Hg too low and show an average scatter of ±8 mm Hg, and (3) that auscultatory diastolic pressures taken at the point of dulling of the sounds average about ±8 mm Hg too high The latter value probably represents the mean error in individual readings of systolic and diastolic pressures when the pressures are measured in a resting subject For most clinical purposes, this error is insignificant Errors in the use of the sphygmomanometer can be minimized by following standard procedures, such as those set forth by a committee of the American Medical Association (1951)

NORMAL BLOOD PRESSURE VALUES IN MAN

Countless numbers of determinations have been made to establish the "normal" values of blood pressure in man Subjects of different sex, age, race, etc, life insurance applicants, school children, university students, army recruits, prisoners, etc, have been examined

Considerable individual differences are found. In groups of the same age, body build, and occupation, one individual will be apparently "normal" with a systolic pressure of 100 mm Hg, and another, equally healthy, individual will have a systolic pressure of 125 mm Hg or higher Patterns of blood pressure are frequently seen which are highly individual. Average figures, it should be emphasized, thus have only a relative value, and statistical studies, while of interest in a general study of blood pressure, indicate only that the blood pressure of an individual has a statistical probability of being "normal"

Table 2-4 illustrates the mean and range in systolic and diastolic blood pressures at different ages and in the two sexes. The data were calculated from 15,706 persons and can be taken as representative of the results of many similar studies It will be seen that mean systolic and diastolic pressures increase with age in both sexes Average systolic readings for *men* show a fairly smooth progression up to the age of 50, after that, the increase accelerates For *women*, the increase in the averages by age is somewhat less smooth than it is for men, but it also is accelerated after the age of 50 The beginning of *menstruation* does not seem to influence the levels of blood pressure of young girls. Nonmenstruating adolescent girls may have relatively higher pressures, but this is probably because of their usual gain in weight *Pregnancy*, when uncomplicated, does not produce significant changes in either systolic or diastolic pressures A recent study (Masters et al, 1956) (Table 2-4) showed that average systolic pressures no longer continue to rise with age in males after 65, nor in females after 70 to 74 years of age. They remain constant to 85 and then decline Female pressures exceed male by 14 mm Hg at age 70 to 74, but over the age of 90, the values approach each other Diastolic pressures show no sex difference and decline slightly after 85 years of age The data indicate that 95 per cent of apparently healthy males over 65 years of age will have systolic pressures ranging from 100 to 190 mm Hg and diastolic pressures of 62 to 102 mm Hg (mean = 145 and 82 mm, respectively) Values for females were computed as 100 to 212 mm Hg for the range of systolic pressure (mean = 156 mm Hg) and 55 to 112 mm Hg for diastolic pressure (mean = 84 mm Hg)

In general, there is no consistent relationship

[1] Insertion of a needle in the brachial or femoral artery, introduction of a catheter into it and advancement of the latter to the aortic arch, and recording of aortic pressure by means of a strain gage, is now current procedure in laboratories of catheterization. *Editor*

between *height* and blood pressure. On the other hand, *weight* is an important and consistent factor in blood pressure changes. Regardless of age or sex, there is progressive increase in the averages of systolic and diastolic pressure with increasing weight.

The limits of "normal" blood pressure have been widely discussed. The upper limits suggested by early studies seem to be too low, and there has been a tendency to raise this limit in line with more recent data (Table 2-5) (see also Phillips, 1956; and Kagan et al., 1956). It should be again emphasized that in any diagnosis of abnormal blood pressure, the whole clinical picture must be considered. Readings which reach or exceed the limits should serve chiefly to alert the examiner to the possible presence of disease. Persistence of high or low values for relatively long periods should be considered significant.

Effect of Race, Climate, and Environment. Most of the available evidence indicates that *Negroes* of the United States have a higher incidence of hypertension than white persons of the same age groups. In general, however, climate and environment seem to be more important than racial origin in determining blood pressure levels. Thus, *Americans* living in China have lower pressures like those of the Chinese, whereas *Chinese* living in this country for any length of time have pressures within the same range as Americans.

A recent study of 3,508 students (Szent-Gyorgyi, 1956) has shown some interesting differences between American and foreign-born students. Using 140 mm systolic and 90 mm

TABLE 2-4 SYSTOLIC AND DIASTOLIC BLOOD PRESSURE READINGS BY SEX AND AGE

Sex and age	Systolic *			Diastolic *		
	Mean	Standard deviation	Coefficient of variation	Mean	Standard deviation	Coefficient of variation
Males:						
16	118.4	12.17	10.28	72.9	10.33	14.17
17	121.0	12.88	10.64	74.4	9.36	12.58
18	119.8	11.95	9.97	74.4	10.03	13.48
19	121.8	14.99	12.31	74.6	10.29	13.79
20–24	122.9	13.74	11.18	76.0	9.93	13.07
25–29	125.1	12.58	10.06	77.8	8.98	11.54
30–34	126.1	13.61	10.79	78.5	9.68	12.33
35–39	127.1	14.20	11.17	80.4	10.42	12.96
40–44	129.0	15.07	11.68	81.2	9.53	11.74
45–49	130.0	16.93	13.02	82.0	10.81	13.18
50–54	134.5	19.21	14.28	83.4	11.31	13.56
55–59	137.8	18.80	13.64	84.0	11.40	13.57
60–64	141.8	21.11	14.89	84.5	12.36	14.63
Females:						
16	116.1	12.10	10.42	72.3	9.55	13.21
17	116.0	11.51	9.92	72.0	9.16	12.72
18	116.3	11.42	9.82	71.8	8.60	11.98
19	115.1	11.87	10.31	71.1	8.93	12.56
20–24	115.7	11.83	10.22	71.7	9.67	13.49
25–29	116.8	11.43	9.79	73.7	9.05	12.28
30–34	119.8	13.97	11.66	74.9	10.78	14.39
35–39	123.9	13.85	11.18	78.0	10.01	12.83
40–44	127.0	17.07	13.44	79.5	10.60	13.33
45–49	130.6	19.47	14.91	81.5	11.63	14.27
50–54	137.3	21.29	15.51	83.5	12.36	14.08
55–59	138.5	21.40	15.45	83.5	11.72	14.04
60–64	144.0	22.33	15.51	85.0	12.95	15.24

* Blood pressure readings in millimeters of mercury.

SOURCE: Master et al., 1950.

diastolic pressure as the upper limit of normal, analysis showed that all racial groups of American students had a significantly higher incidence of hypertension than comparable foreign-born male groups. After 10 years of residence in the United States and Canada, foreign-born students have the same high incidence of hypertension as those born in the United States and Canada. It was concluded "One gets the impression that if someone lives in the United States long enough—regardless of birthplace or race—he will stand the same chance of becoming hypertensive as if he had been born here."

Factors Influencing Levels of Pressures. It may be useful to consider the significance of changes on systolic, diastolic, and pulse pressures in terms of factors which influence them. The *systolic pressure* is subject to wider variations under ordinary conditions of health than the diastolic pressure and particularly reflects changes in cardiac output or distensibility of the walls of the aorta or large arteries. *Diastolic pressure*, on the other hand, is a reflection of the constant load which the vascular walls are carrying throughout the arterial system, and is a reliable index of the state of the more peripheral vessels. Situations which concomitantly alter the cardiac output and peripheral resistance would be expected to change systolic and diastolic pressures. Thus, the two pressures rise when blood volume is increased with the resultant distention of the arterial system and increase in cardiac output. Likewise, where the

TABLE 2-5. NORMAL RANGE AND LIMITS OF HYPOTENSION AND HYPERTENSION

Age, years	*Systolic* *			*Diastolic* *		
	Hypotension, upper limit	*Normal range*	*Hypertension, lower limit*	*Hypotension, upper limit*	*Normal range*	*Hypertension, lower limit*
Males						
16	98	105-135	145	52	60-86	90
17	98	105-135	145	55	60-86	90
18	98	105-135	145	55	60-86	90
19	98	105-140	150	55	60-88	95
20-24	98	105-140	150	56	62-88	95
25-29	100	108-140	150	60	65-90	96
30-34	100	110-145	155	60	68-92	98
35-39	102	110-145	160	60	68-92	100
40-44	102	110-150	165	60	70-94	100
45-49	104	110-155	170	60	70-96	104
50-54	105	115-160	175	60	70-98	106
55-59	106	115-165	180	60	70-98	108
60-64	108	115-170	190	60	70-100	110
Females						
16	95	100-130	140	55	60-85	90
17	95	100-130	140	55	60-85	90
18	95	100-130	140	55	60-85	90
19	95	100-130	140	55	60-85	90
20-24	95	100-130	140	55	60-85	90
25-29	98	102-130	140	55	60-86	92
30-34	98	102-135	145	55	60-88	95
35-39	100	105-140	150	60	65-90	98
40-44	100	105-150	165	60	65-92	100
45-49	100	105-155	175	60	65-96	105
50-54	105	110-165	180	60	70-100	108
55-59	105	110-170	185	60	70-100	108
60-64	105	115-175	190	60	70-100	110

* Blood pressure readings in millimeters of mercury.
SOURCE Master et al, 1950

between *height* and blood pressure. On the other hand, *weight* is an important and consistent factor in blood pressure changes. Regardless of age or sex, there is progressive increase in the averages of systolic and diastolic pressure with increasing weight.

The limits of "normal" blood pressure have been widely discussed. The upper limits suggested by early studies seem to be too low, and there has been a tendency to raise this limit in line with more recent data (Table 2-5) (see also Phillips, 1956; and Kagan et al., 1956). It should be again emphasized that in any diagnosis of abnormal blood pressure, the whole clinical picture must be considered. Readings which reach or exceed the limits should serve chiefly to alert the examiner to the possible presence of disease. Persistence of high or low values for relatively long periods should be considered significant.

Effect of Race, Climate, and Environment. Most of the available evidence indicates that *Negroes* of the United States have a higher incidence of hypertension than white persons of the same age groups In general, however, climate and environment seem to be more important than racial origin in determining blood pressure levels. Thus, *Americans* living in China have lower pressures like those of the Chinese, whereas *Chinese* living in this country for any length of time have pressures within the same range as Americans.

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Sex and age	Systolic *			Diastolic *		
	Mean	Standard deviation	Coefficient of variation	Mean	Standard deviation	Coefficient of variation
Males:						
16	118 4	12 17	10 28	72 9	10 33	14 17
17	121 0	12 88	10 64	74 4	9 36	12 58
18	119 8	11 95	9 97	74 4	10 03	13 48
19	121 8	14 99	12 31	74 6	10 29	13 79
20–24	122.9	13 74	11 18	76.0	9 93	13 07
25–29	125 1	12 58	10 06	77 8	8 98	11 54
30–34	126 1	13 61	10 79	78 5	9.68	12 33
35–39	127 1	14 20	11 17	80 4	10 42	12 96
40–44	129 0	15 07	11 68	81 2	9 53	11 74
45–49	130 0	16 93	13 02	82 0	10 81	13 18
50–54	134 5	19 21	14 28	83 4	11 31	13 56
55–59	137 8	18 80	13 64	84 0	11 40	13 57
60–64	141 8	21 11	14 89	84 5	12 36	14 63
Females.						
16	116.1	12 10	10 42	72 3	9 55	13 21
17	116 0	11.51	9 92	72 0	9 16	12 72
18	116 3	11 42	9 82	71 8	8 60	11 98
19	115 1	11 87	10 31	71 1	8 93	12 56
20–24	115 7	11 83	10 22	71 7	9 67	13 49
25–29	116 8	11 43	9 79	73 7	9 05	12.28
30–34	119 8	13 97	11 66	74 9	10.78	14 39
35–39	123 9	13 85	11 18	78 0	10 01	12 83
40–44	127 0	17 07	13 44	79 5	10 60	13 33
45–49	130 6	19 47	14 91	81 5	11 63	14 27
50–54	137 3	21 29	15 51	83 5	12 36	14 08
55–59	138.5	21 40	15 45	83 5	11 72	14 04
60–64	144 0	22 33	15 51	85 0	12 95	15 24

* Blood pressure readings in millimeters of mercury.
SOURCE: Master et al., 1950.

cally active neurons of the *pressor area*. It is also well known that there are areas in the *hypothalamus* which, when stimulated, cause striking changes in the arterial pressure and heart rate. The *cerebellum* may also act through the hypothalamic and bulbopontine areas to influence vasomotor control, as may various parts of the cerebral cortex. The motor and premotor cortex influence is predominantly directly on the spinal cord sympathetic centers.

Although attractive and usually discussed in many texts, the hypothesis of Bayliss of a reciprocal control of blood vessels by way of specific vasoconstrictor and vasodilator centers in the medulla must be abandoned. No true vasomotor reflexes can be seen after sympathectomy, rendering unlikely the concept that dorsal root vasodilator fibers and the parasympathetic nerves form the efferent pathways from the postulated vasodilator center. Sympathetic vasodilator fibers are not engaged in the reflex (presso- and chemoreceptor) control of vascular tone, nor do parasympathetic vasodilator fibers participate in the control. This common type of centrally induced vasodilatation is caused simply by an *inhibition of constrictor tone*. Thus, the principal neurogenic control of the peripheral circulation is the increase or decrease in vasoconstrictor tone. Sympathetic vasodilator fibers have been described and seem to be distributed only to vessels of the skeletal *muscles*. It is questionable whether they are involved in blood pressure homeostasis.

In discussing the control of blood pressure, emphasis is usually placed on the neurogenic control of arteriolar tone via the sympathetic nerves. Little is said of what must be an important factor, viz., *venous tone*. This is perhaps because we have so relatively little direct information as to control of venous tone. It is assumed that sympathetic stimulation will act on venules as it does on arterioles. This is an important consideration in view of the reservoir function of the veins as compared to arteries.

The many factors concerned in the behavior of veins have been discussed by Brecher (1956b). He summarizes the problem of venous tone as follows: "Veins have a relatively low distensibility upon transient increases in intravascular pressure. Their smooth muscles contract actively upon adrenergic and reflex stimulation and contribute considerably to circulatory adjustments. Pooling of blood in the splanchnic venous system occurs due to passive yielding of the venous walls upon prolonged action of intravascular pressures, physiological reflex venodilation and failure of the venomotor mechanism in irreversible hemorrhagic shock." He also summarizes factors affecting venous return. "The entire venous system becomes dilated but less distensible upon cholinergic stimulation, whereas it is constricted but elastically more distensible under adrenergic influence. Central systemic veins and the pulmonary vascular bed represent variable blood depots which are readily available for increase in heart inflow and output sudden demand. In normal recumbent man the large blood reservoir in lung and heart is immediately utilized during sudden physical work or positional change to increase left stroke volume before systemic venous return can be increased appreciably. When the thoracic blood reservoir is reduced in anesthesia or by trauma, the output of the left heart depends directly upon fluctuations of systemic venous return. Reflexes from stretch receptors in the venous walls may aid in regulating heart output, the total circulating fluid volume and arterial inflow into local venous beds."

Receptors which, when stimulated, will modify the blood pressure have been located in many parts of the body, particularly in the pulmonary, innominate, and subclavian arteries, and in the arch of the aorta and the internal carotids slightly above the bifurcations of the common carotid (*carotid sinus*). Recent studies in the cat have shown five areas of the common carotid which are sensitive to pressure changes (four on the right and one on the left). These show histologic patterns of nerve structure similar to that of the carotid sinus and other sensitive areas. In each area, the myelinated fibers of the pressoreceptor nerves ramify in the adventitia. In the carotid sinus area, nerve fibers enter the media from the adventitia. Structural modification of the arterial wall is always seen at receptor sites.

These receptors are commonly referred to as presso- or baroreceptors, since they are stimulated by changes in blood pressure. Since blood flow to the brain is *primarily a function* of the systemic blood pressure, it may be argued on teleologic grounds that these reflexes are strategically placed in the upper part of the body to minimize changes in cerebral *circulation*. A rise in pressure in the aorta or carotid sinus elicits impulses via vagal *afferents* and the nerve of Hering, respectively, which serve to inhibit vasomotor activity, whereas a fall in aortic or carotid sinus pressure results in fewer

peripheral resistance and cardiac output are low, as in shock, both pressures drop

If only *stroke volume increases* and all other factors remain reasonably constant, the systolic pressure is raised. The diastolic pressure change is minimal, and consequently the pulse pressure increases. As a result of the high pressure at the end of the ejection phase, the pressure gradient throughout systole is steeper and more energy is expended in giving velocity to the blood. Thus, a large proportion of the blood will have passed through the arterioles by the end of diastole. An *increase in heart rate* not accompanied by an increase in cardiac output or peripheral resistance may be expected to cause changes chiefly in diastolic pressure. The diastolic period is shortened, and less time is therefore allowed for the energy stored in the elastic walls during systole to become converted into energy of flow during diastole; i e., the fall in pressure during diastole is stopped at a higher level by the earlier arrival of the next beat. A *decrease in heart rate* will have the opposite effect Systolic pressure changes minimally as long as the cardiac output remains reasonably constant.

Since, as previously indicated, diastolic pressure represents the constant load imposed by the arterial system, any factor which alters this load would be expected to influence the level of diastolic pressure Widespread *dilatation* and consequent decrease in peripheral resistance would result in a lower diastolic pressure. A fall in *blood viscosity* would have the same effect, as would *aortic regurgitation* In the latter situation, an increased quantity of blood passes from the arterial system during diastole as a result of the leakage through the incompetent aortic valves *Loss of arteriolar elasticity* would be expected to lower diastolic pressure. Here, however, the results may be variable If, as is often seen in arteriosclerosis, the narrowing extends to the peripheral vessels, the diastolic pressure will be high On the other hand, if the sclerotic changes involve only the larger vessels and their branches while the smaller peripheral vessels are not narrowed (atherosclerosis), the diastolic pressure will be lowered (and the systolic pressure will be high).

Posture produces variable changes in systolic pressure The systolic pressure in an upright individual may be a few millimeters higher or lower or may be the same as the pressure in the recumbent position. The diastolic pressure, however, is usually 5 or 10 mm Hg higher. Prolonged quiet standing leads to an eventual fall in systolic pressure while the diastolic pressure remains high. The pulse pressure narrows considerably. The raised diastolic pressure is unquestionably the reflection of increased peripheral resistance resulting from compensatory vasoconstriction mediated by the carotid sinus reflex. The systolic pressure will be maintained only as long as this mechanism is able to compensate for the tendency of the cardiac output to drop because of diminished venous return occasioned by the pull of gravity.

If and when the *cardiac output diminishes significantly,* compensatory vasoconstriction can no longer sustain the systolic pressure and syncope may occur. The pattern of change with posture is more labile in old (60 years or older) than in young individuals.

CONTROL OF MEAN ARTERIAL BLOOD PRESSURE

Arterial pressure is controlled by three major control mechanisms. (1) nervous, (2) hemodynamic, and (3) chemical or hormonal. These mechanisms serve to minimize fluctuations in blood pressure under changing physiologic conditions such as posture, exercise, and sleep, as well as under temporarily abnormal conditions such as blood loss, trauma, etc

Nervous (Vasomotor) Control. Structures in the medulla are primarily responsible for vasoconstrictor fiber tone, and the continuous discharge goes on in a normal chemical environment even after elimination of all incoming nervous influences In this sense, these neurons may be said to exhibit an automaticity, and their activity is moderated by impulses from presso- and chemoreceptors Because of this relative independence from higher-level control, this area is generally designated as the *vasomotor center,* although it is not strictly localized but consists of a diffuse network of interconnected neuron groups in the reticular formation extending from the lower parts of the pons to the obex Exploration of the brain stem by localized stimulation also shows the presence of a *depressor area,* and it may be assumed that the two areas can act as a functional unit, with the depressor area integrating inhibitory influences with a secondary influence on the toni-

the other hand, the injection or infusion of small amounts of epinephrine or norepinephrine in doses which might be assumed to be similar to amounts elaborated by the adrenal medulla produces equivocal results on the blood pressure in man Initial vasoconstriction may be followed by dilatation, or there may be only dilatation and a fall in blood pressure Differences are seen in the effects of epinephrine and norepinephrine on vessels in different parts of the body The effects of these substances on the peripheral and central nervous system are yet to be fully clarified The same is true of possible central control of the adrenal medulla The available evidence suggests that the importance of these catechol hormones for the "motor" control of blood vessels is quite insignificant as compared with direct vasomotor innervation

Considerable interest has been shown in the literature in the presence of various humoral substances in the brain circulation and their possible effects on the activity of the vasomotor center The roles of acetylcholine, serotonin, cerebrotonin, and substance P (a smooth muscle stimulator of polypeptide structure) in this regard and in the maintenance of "normal" blood pressure, still remain to be elucidated (Page, 1957).

In summary, the blood pressure level in a given patient at a given time is maintained by the interaction of a variety of mechanisms. The composition of the blood, humoral mechanisms, reflexes, and impulses from higher levels influence the vasoconstrictor areas and so modulate the resistance of blood vessels. Equally important are, (1) the amount of blood actively circulating in the blood stream in relation to the capacity of the vascular tree, and (2) the levels of venous return and cardiac output. In this respect, the heart occupies a key position As servant of the circulation it must be able to accept an adequate amount of blood from the veins and eject an adequate amount of blood into the aorta to meet the particular demands of the organism

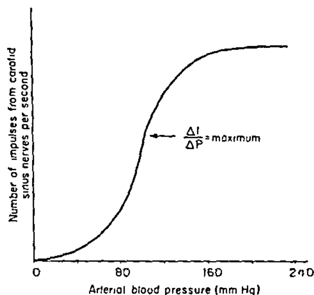


Fig. 2-49. Response of pressoreceptors to arterial blood pressure. (*From Guyton, 1956.*)

inhibitory impulses being transmitted and so allows vasoconstriction to take place. The relationship of blood pressure and impulses is shown in Fig. 2-49 It will be seen that the change in number of impulses per second for each unit of pressure ($\Delta I/\Delta P$) is greater at about the level of usual mean blood pressure A slight change in blood pressure from this level will cause a relatively great change in the number of impulses passing to the medulla and a consequent readjustment of sympathetic tone. Heymans and his group, who did the pioneer work in this field, have suggested that the changes in tone and tension of the pressosensitive arterial walls, and not pulsatile expansion, play a primary and fundamental role in the mechanisms of reflex homeostasis of blood pressure. They showed that local application of norepinephrine to the arterial walls of the carotid sinus induced a marked reflex fall in blood pressure, although the carotid sinus walls were deprived of pressure and pulsatile expansion. These and other experiments led to their suggestion that *a decrease in tone and resistance to stretch of the walls of the arteries where receptors of moderator nerves are located could be the primary mechanism of essential hypertension.*

Hemodynamic Control. Blood volume is an important factor in the control of blood pressure, since it is axiomatic that the blood volume and the capacity of the vascular bed must always be the same The elastic bed may be distended at a greater or less pressure, but empty spaces are inconceivable, and any change in the size of the vessels must be associated with a corresponding change in blood volume, otherwise it must be assumed that any enlargement of one set of vessels is exactly balanced by an equal reduction in the size of other vessels Although reflex control probably plays the major role in rapid adjustments, alteration in *blood volume* is part of the usual mechanism. Capillary and osmotic pressure relationships between the vascular and extravascular system, determinants of blood volume, thus become important factors in determining levels of mean blood pressure. If capillary pressure is raised by the infusion of large amounts of blood or other solutions, there is a transudation of dilute plasma to the extravascular system so that mean arterial pressure changes minimally or not at all. On the other hand, hemorrhage is accompanied by an inflow of fluid which serves to increase the blood volume and mean arterial pressure. This ability to shunt fluid back and forth from the extravascular system acts as an effective control of mean blood pressure, supplementing nervous control

Over the past years, consistent reports have strongly suggested that *sodium* is implicated in the pathogenesis of hypertensive states Sodium retention and consequent increase in the extracellular fluid volume would be expected to increase the cardiac output, but this does not occur The increased blood pressure is presumably the result of increased peripheral resistance, and the suggestion has been made that the latter effect is due to "sodium transfer systems" which govern the entrance and extrusion of sodium, potassium, and water in vascular smooth muscle. Entrance of sodium causes the muscle to swell, thus increasing the resistance and elevating the pressure It remains to be shown conclusively whether this mechanism is important in blood pressure homeostasis.

Chemical and Humoral Control. It has generally been assumed, though never definitely proved, that the hormones secreted by the adrenal medulla markedly contribute to the vasomotor control of blood vessels and thus serve to regulate the level of blood pressure. The adrenal medulla is known to secrete *epinephrine* and *norepinephrine* Histologic studies suggest the presence of two types of cells, epinephrine cells and norepinephrine cells. On

drugs (Remington et al, 1945) (Fig. 2-50A, line C) and significantly smaller with constrictor drugs (Remington, 1952) (*Fig 2-50A, line A*).

Since V is relatively inaccessible to measurement in the live animal and $\Delta P/\Delta V$ can be derived from the stroke volume and pressure pulse, the latter is a much *more useful* physiologic concept than relative distensibility ($V\Delta P/\Delta V$).

Ejection *from the heart is not*, of course, continuous If the *ejection, still remaining* constant and slow as before, were broken up into intermittent pulsations, arterial pressure would rise during *ejection in accordance with* $\Delta P/\Delta V$ at the particular pressure *range* between pulsations (Fig 2-50B, broken line).

Arteriolar drainage or runoff modifies the relation between *ejection* and increment in pressure. Let us assume that drainage is allowed in such a manner that the pressure rises from 80 to 120 mm Hg during systole and falls during diastole to 80

It seems clear that when pressure *is high*, runoff must be greater than when it is low. Indeed runoff *ceases* when pressure falls to about 20 mm Hg (Whittaker and Winton, Burton, 1954) and is roughly proportional to pressure height above 20 mm Hg

Assuming drainage proportional to pressure minus a constant, the effect of ejection would be modified as diagramed by the solid line in Fig 2-50B (ejection *is still* assumed to be slow and constant) Subtracting *drainage* would cause the volume in the arterial tree to *increase* less rapidly and the pressure slope to be less steep Moreover, the effect of drainage becomes more pronounced as the pressure *rises* and the slope becomes gradually less and less When ejection has ceased, *drainage*, which is still proportional to pressure, *results in* a rapid pressure fall at first, which gradually becomes less and less steep

Considerations so far described lead to the possibility of evaluating the drainage *during* systole in terms of the *distensibility of the arterial tree* (Hamilton and Remington, 1947) The drainage during diastole equals the arterial uptake during systole, which, as will be seen below, can be derived from the stroke volume or empirically measured The total systolic ejection (*stroke volume*) is the sum of the blood which distends the arteries (arterial uptake) and that which runs off through the arterioles during systole.

This last quantity, systolic drainage, Ds, equals the uptake, U, times the ratio of systolic and diastolic drainage. Since each is proportional to the time-pressure product, minus a constant, i.e., the area of the systolic part of the pulse curve, As, and the area of the diastolic part of the pulse curve, Ad, the systolic drainage may be computed as $Ds = (As/Ad)U$.

Outlined above are the *relations of ejection* and drainage that might occur when the arterial tree is thought of as filling simultaneously. In *reality*, ejection is so quick that the proximal parts of the aorta are filled to a considerable pressure before the pulse wave has traversed the artery very far. This results in a decided steepening of the initial upstroke of the curve (Fig. 2-51A).

The steepening of the *initial parts* of the curve is due to two factors. In the *first place*, the column of blood in the upper parts of the aorta is nearly stationary, and appreciable pressures are needed to move this column of blood sufficiently to expand the lower parts of the aorta and raise the pressure therein. The first small part of ejection expands only the very upper part of the aorta and produces a pressure

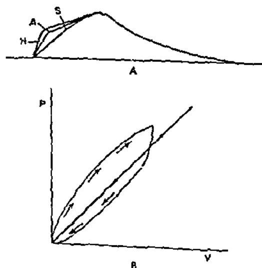


Fig 2-51 A Pulse ... rapid filling of viscoelastic tube. B Relation of pressure, P, to volume, V, with rapid → → and slow —— stretch

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The arterial pulse

WILLIAM F. HAMILTON

In a normal adult with an average heart rate, every time the heart beats, it ejects about 80 ml of blood into the aorta Such ejection increases the pressure in the arterial system from 80 to 120 mm Hg. This increase in pressure is seen first in the great arteries near the heart, and is propagated as a *pulse wave* in the whole arterial system, arriving at the terminal arterioles usually before ejection has ceased.

Details of the magnitude and shape of the pulse curve and of the transformation from its *central* to its *peripheral* contour are dependent on conditions and circumstances that have important physiologic implications and are subject to at least partial analysis.

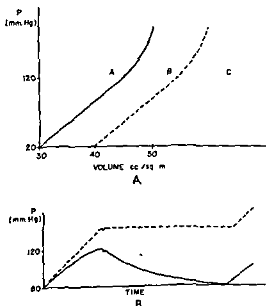


Fig. 2-50. A. Pressure-volume relations of the arterial system. A, constricted; B, normal, C, dilated (diagrammatic). B. Effect of a constant slow injection without drainage (broken line) and with drainage (solid line.)

The analysis may be started on the following simplifying assumptions: (1) that the ejection is at a constant rate; (2) that it is slow, so that the peripheral and central parts are distended at approximately the same time; and (3) that drainage out through the arterioles and into the veins does not occur. The large arteries thus constitute in effect a simple closed elastic chamber.

With these assumptions, the rise in aortic pressure is simply a function of the changing elasticity of the arterial wall. At first, as a constant stream is injected into the artery, the pressure rises at a constant rate, from, say, 20 to 120 mm Hg Equal increments of volume result in equal increments in pressure. Above a pressure of 120 mm Hg, the artery becomes less distensible and the increments in volume produce a larger increment in pressure (Fig. 2-50A, line *B*).

Two things must be emphasized in this description It is not a description of the relative change in volume with pressure change, and it has no relation to Young's modulus It is a description of the absolute, not the relative, volume change Expressed mathematically, it is a reference to the relation $\Delta P/\Delta V$, and not to the modulus which is used by physicists to describe the elasticity of materials, $V \Delta P/\Delta V$

The simple increment in pressure with increment in volume is a quantity that is relatively independent of the total capacity of the arterial bed, which is usually larger at a given pressure with age, hypertensive history, and vasodilator

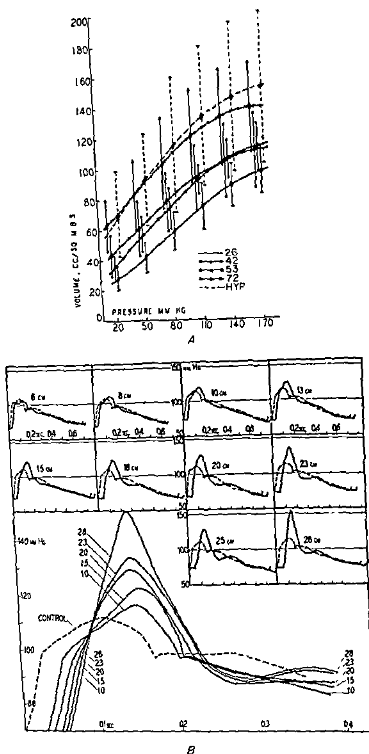


Fig 2-53 A. Influence of age on the volume-pressure relations of human aortas Each curve represents average values for each age group Vertical lines represent standard deviations B Reconstructions of aortic pressure pulses showing comparison between control in the aortic arch (dotted lines) and records taken simultaneously with their controls at indicated distances down the aorta from the arch (solid lines). Below are 5 of the above 10 figures semidiagrammatically superimposed

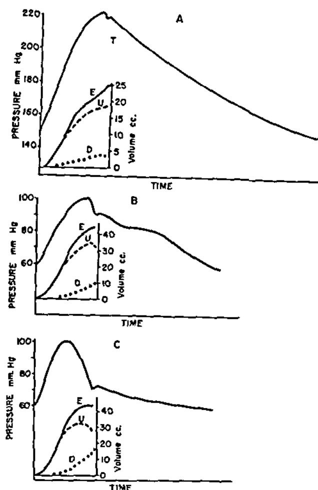


Fig. 2-52. Typical cardiac ejection curves (see Remington and Hamilton, 1947, for method of calculation from arterial uptake and arteriolar drainage) A Pulse of a dog with renal hypertension The pressure and resistance were high, the drainage and stroke volume were low, ejection was continuous. B. Large stroke volume Pressure and resistance and drainage intermediate, ejection slow toward end of systole. C. Large stroke volume, mean pressure low, resistance low, drainage high, ejection stops toward end of systole

rise that is much greater than if the whole of the aorta were distended by the same volume Later in systole, when the lower parts of the aorta are being distended as the pulse wave is transmitted down, the pressure (distention) of the upper parts will reach an equilibrium between blood leaving and entering the upper aorta.

Secondly, careful measurements of the pressure-volume and pulse-wave transmission in a model indicate that pressure is generated in greater amount than can be accounted for by the distention of a rubber tube or aorta as measured at slow rates of distention. This excess pressure is confined to the initial part of the pulse and may be qualitatively explained by the fact that all elastomeric materials (rubber, arteries, etc.) are more resistant to rapid than to slow stretch (*hysteresis*). The effect of hysteresis is indicated in Fig. 2-51A by *H*, as distinguished from the effect of restriction of initial distention to the upper aorta, which is indicated by *A*. The relation of pressure to volume in rapid and slow stretch is given in Fig. 2-51B.

Not only does the aorta contribute to the shape of the systolic part of the pulse wave in the manner just described, but the heart varies the rate and time course of ejection Figure 2-52 gives typical examples of ejection curves and of the pressure pulse curves which result (For method of calculating ejection curves see Remington and Hamilton, 1947.)

Transmission of the Pulse Wave. It has long been known that the pulse wave is transmitted more slowly in more distensible tubes and more rapidly in more rigid tubes Mathematic equations have been proposed by Moens, Korteweg, and Bramwell and Hill to express quantitatively the relation between pulse-wave velocity and relative distensibility. The most convenient to use with ordinary measurements of pressure is that of Bramwell and Hill, which is as follows.

$$pwv = 0.357\sqrt{V\Delta P/\Delta V}$$

where pwv = the pulse-wave velocity, in meters per second

ΔP = the rise in pressure, in millimeters of mercury corresponding to ΔV, the increment in volume starting from V, the diastolic volume of the tube segment concerned

This relationship has been used by Broemser and Ranke, Wezler and Boger, Bazett et al., 1935, and many others to predict the arterial distensibility, and, from this and the pulse pressure, to predict the stroke volume *This approach has not received wide acceptance and possesses two theoretical disabilities* One is that the pulse-wave velocity measures the relative distensibility and requires knowing the volume of the aorta at diastolic pressure. As seen from Fig 2-52, this is a highly variable measurement Not only does it vary with age, pressure (Fig. 2-53A), and pathologic history, but also with the physiologic condition at the moment. Since pulse-wave velocity measures arterial dis-

of reflection and superimposition can be used to explain an augmentation of the peripheral pulse pressure to a value that is more than twofold the central pulse pressure.

Quantitative Aspects. Since early times (Erlanger and Hooker), many workers have estimated the stroke volume from the pulse pressure This work was mostly done in man and lacked quantitative control. In an attempt to evaluate in the dog the physiologic changes in arterial distensibility from the relation of pulse pressure to stroke volume, it was found that arterial distensibility, when measured as absolute uptake per millimeter of mercury per square meter of body surface (stroke index), showed very little variation under widely different conditions This uniformity was so marked that it was decided to try to develop an empirical method for accurately relating the stroke index to the pulse pressure The procedure, which cannot be described here in detail, was roughly to divide the arterial bed into four regions (1) arch, (2) head, forelegs, and thoracic arteries, (3) abdominal and visceral arteries, and (4) hind leg arteries The distensibility of these separate beds was measured

The transmission time of the pulse wave to each of these regions was also measured, so that a point could be picked out on the pulse curve that would give the pressure and the degree of distention (uptake) in the several beds at the time of closure of the valves The uptake of the different beds could then be added together, and drainage calculated as indicated above. *Uptake and drainage together give the stroke index*

The degree with which the stroke index, as measured in this manner (both by the original authors (Hamilton and Remington) and in independent laboratories], matches that meas- [illegible] the arterial bed into very small segments, an analogous calculation can be made which gives a quantitative description of the cardiac ejection curve (Fig 2-52)

There are conditions in which the pulse-contour method gives too high a stroke volume These are marked by a distorted pulse that is easily recognized

Since human aortas are much more variable, through the effects of age and disease, than are dog's arteries, one cannot justify *in man the elaborate calculation given above for the dog.* Nevertheless, empirical relationships have been tabulated (Remington et al, 1948) which enable one to predict stroke volume from brachial pulse pressure. At arterial pressures below 120 mm Hg, 1 mm pulse pressure = 1 ml stroke volume per square meter (stroke index). At higher pressures, the figure for stroke index is less. Excluding patients with congestive failure (whose index seems to be overestimated), the correlation between stroke volume as measured in this way and by the Fick procedure is $R = 0.79$, and the average error is 18 per cent.

Pulse Form in Certain Abnormalities. In *aortic stenosis*, ejection is slowed, the systolic pressure is built up gradually, the oscillatory phenomena are suppressed, and the augmentation of the pulse pressure is minimized while systolic vibrations of pressure due to turbulence are manifest.

In *aortic regurgitation*, rapid diastolic drainage through the open aortic orifice causes the pulse pressure to be large as a result of a low diastolic pressure The large *ejection, combining* tidal volume with stroke volume, causes an increase in systolic pressure resulting in a

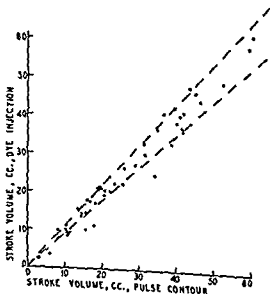


Fig 2-54. Relation between the stroke volume of dogs, as measured by the dye injection technique and as calculated from simultaneously taken pressure-pulse contours. The broken lines represent a deviation of 10 *per cent* from the line of identity

tensibility as a fraction of this unknown and highly variable quantity, it is a useless step in measuring arterial uptake in milliliters per millimeter of mercury of pulse pressure.

A second disability of pulse-wave velocity as a step in stroke volume measurement is the fact that the pulse wave is propagated at a velocity which is determined by the relative distensibility at the time of the initial upstroke of the pulse curve. At this point, the rapidity of distention results in a rigidity, due to hysteresis, that gives a pulse-wave velocity that is falsely fast in terms of arterial uptake over the whole of systole. Moreover, the sluggish return of volume to that corresponding to diastolic pressure will give an unpredictably high pulse-wave velocity at rapid heart rates.

Changes in Pulse Form During Transmission. The details and quick movements of the central pulse curve are usually lost as the pulse traverses the upper part of the aorta, so that the curve is a fairly smooth undulation in the iliac and femoral Among the finer elements thus lost is the incisura, which is made by the closure of the aortic valves.

A striking change which occurs as a result of the transmission of the pulse wave is *the increase in the pulse pressure as the pulse wave passes out to the periphery* The simplest example of this is the *standing wave system* in the dog's aorta It is called a "standing wave" because the peaks of the wave train are simultaneous below a certain region in the thoracic aorta and there are undulations above this "nodal" region that are 180° out of phase with these peaks (Fig 2-53B).

In explanation of this phenomenon, it was held that somewhere about the knee, reflection occurs at the arterioles and the wave doubles back on itself, thereby augmenting its height A similar, though much lesser, reflection takes place at the root of the aorta There is thus an oscillating system with maximum pressure changes at the two ends and maximum velocity changes at the node A system of standing waves can be *displayed more clearly by* occluding the lower aorta by inflating a balloon in its lumen. The reflection takes place in one location instead of being the diffuse summation of minute reflections from many arterioles whose average distance from the heart is that of the knee.

It is curious that a wave is reflected in a positive sense when the aggregate cross area of the arterioles is greater than that of the aorta itself. If such dimensional considerations were significant, one would expect to find branchings where the pulse wave disappeared completely with a resulting negative reflection. However, the arterioles act as a stop to flow, a site of resistance. Because of their small individual size, they give rise to high frictional energy loss (see Poiseuille's law in Part 2, Chap. 9). An illustrative model would be a distensible rubber tube with a one-hole stopper in the end. This stopper is the site of slow drainage, high frictional loss, and reflection of a positive wave. A bundle of capillary tubes whose aggregate cross areas total more than the main tube, and whose resistance is also greater, would be an interesting model if substituted for the stopper described above.

The fact that arteriolar dilatation alters the *system of standing waves* and the augmentation of the pulse pressure in the femoral artery is further evidence that *the constricted arterioles are the site of reflection.*

The pulse pressure can be augmented almost to twice its central value by the reflected-wave system However, it may happen that the pulse pressure in the femoral artery or in the dorsalis pedis is more than twice that in the aorta. This may be the result of the summation of augmentation of the pulse pressure by reflection, with or without a standing wave, and of beat-to-beat resonance, as seen below.

When the pressure pulse is mapped out in the human brachial artery and in the human aorta, it is seen that the peak, as well as the start, of the wave is usually propagated In other words, there is no clear standing wave system None the less, the pulse pressure is augmented as it traverses the artery in question. This may be because, in these vessels, the arterioles are placed more diffusely in time-distance from the heart and hence do not reflect waves with enough simultaneity to set up a *single standing-wave system.*

When the heart rate is rapid and the arterial pressure low, the pulse pressure may be greatly augmented in the periphery This seems to be the result of *superimposing* the systolic rise of a succeeding beat upon the diastolic rise (Fig. 2-53B) of the preceding one The summation

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Physical principles of liquid flow

SIMON RODBARD

The idealized formulas which describe flow through simplified rigid pipes have very limited usefulness in explaining the complex dynamics of the cardiovascular system, derivations and formulations are therefore not given in this section Investigators requiring rigorous formulations, derivations, and analyses of hydraulic relationships are referred to texts on hydraulics, hydrodynamics, and aerodynamics (see Bibliography) Since blood is a nonhomogeneous fluid whose pulsating flow takes place in curved elastic tubes of variable cross sections and numerous irregularly spaced side branches, only the general principles of hydraulics can be useful in describing the circulation Nevertheless, these guiding principles do aid in rationalizing some of the dynamic relationships regulating flow, and are useful in indicating some of the potential roles of mechanical factors on blood vessel structure

Viscosity. A liquid yields continually to the slightest force which tends to divide it along any plane, no matter how small this shearing stress may be. For example, a red blood cell will fall through a column of plasma, "shearing" the liquid in its path

Viscosity is the property of fluid which offers resistance to shear Thus, the rate of fall of a red cell will depend in part on the viscosity of the plasma through which it is falling, being slower in more viscous plasma

Sedimentation. Particles with densities greater than that of plasma tend to *settle* out of the fluid Gravitational pull causes the denser particles to settle more rapidly Thus, agglomeration of red cells into clumps increases their tendency to settle out rapidly. If the particle is very small (the size of red blood cells), settling is markedly slowed by the viscosity of the fluid.

While the settling tendency is diminished in rapidly moving streams (large arteries), settling of cells occurs with greater facility when blood moves relatively slowly. Viscosity is also measured by permitting fluid to flow through pipes. With greater viscosities, less flow will take place for a given pressure head This relation was first studied by Poiseuille, in whose honor the poise, or unit of viscosity, is named. These rules hold quantitatively for water, oils, and other homogeneous fluids However, since blood is a suspension of formed elements in plasma, its behavior differs somewhat from the simpler fluids, i e., it has an *anomalous* type of viscosity.

Pressure. Liquids are *incompressible*, i e., the volume of a fluid, such as blood, does not change significantly when physiologic pressures are applied to it The *pressure* in a fluid is the force acting perpendicularly to a unit surface. This pressure results from the continuous bombardment of the surface by the molecules of the fluid The greater the number of molecules striking the surface in a unit time, the greater will be the pressure. In a static liquid system the pressure is equal at all points on the same horizontal level Pressure increases with depth. thus, the pressure acting on the wall of blood vessels (*lateral pressure*) in dependent parts of the body is greater than at more elevated levels For example, in a standing man the ...

... equal to the difference in the

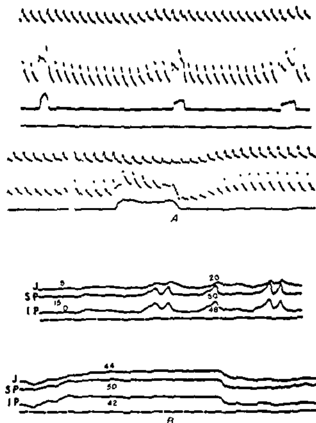


Fig. 2-55. A. Differential pressures during a short elevation (cough) upper records, or longer elevation (strain) lower records of the intrapulmonary pressure. The lower tracing is of sudden expiratory efforts against a resistance, the middle is the effect of this on arterial pressure. Above is the effective distending pressure on the artery within the thorax (Lower record, subtracted instrumentally from middle.) B Jugular, spinal, and intrathoracic pressure during cough and strain.

further increase in pulse pressure. Not only is the pulse pressure large, per unit net stroke volume at the central aorta, but it may be augmented to a greater degree than normal as it passes out to the periphery

In *arterial hypertension*, the excursion of the pulse pressure is over a range in which the artery is less distensible than in the normal range The pulse pressure is hence greater per *unit stroke volume than normal*

In *older people* with less distensible arteries, systolic pressure may be elevated even though diastolic pressure is within normal limits. The small rise in mean pressure indicates a small increase in peripheral resistance. In true hypertensive cardiovascular disease, diastolic pressure is elevated and systolic pressure is elevated still *more.*

Effect of Extravascular Pressure. During a *cough*, the pressure surrounding the great arteries of the thorax and abdomen rises, often as much as 200 mm Hg. This rise is faithfully propagated out the arterial tree, causing the arterial pressure to be augmented by an equal figure. This sudden increase in arterial pressure distends the arteries outside the thorax and abdomen, but within these cavities the arteries are not distended by extra strain because the *adventitious pressure is equal outside and inside.*

The venous pressure rises in phase with the arterial pressure during cough but not nearly so much.

Simultaneous tracings of the cerebrospinal pressure and the intrathoracic pressure during a cough indicate that they go up *identically in time and in pressure.* Transmission of the thoracoabdominal pressure into the cerebrospinal canal is probably through the intervertebral foramens. *Thus the cerebrospinal arteries are* protected against strain during a cough in the same way that the thoracic and abdominal arteries are (Fig 2-55)

in pressure (Fig 2-57, C, D, E). If on the other hand the vessel wall is relatively firm, the pressure will rise sharply when even small volumes of fluid are added Pressure generates tension in the wall of the vessel by causing it to be *stretched* (*strained*). This tension is similar to the strain generated in a wire when a weight is attached to the dependent end In a tube, the tension, *T*, generated in the wall is proportional to the product of the pressure, *P*, multiplied by the radius, R, i e., $T \propto PR$ As a consequence of this relationship, injection of fluid into a distended vessel increases the tension in the wall in two ways, since (1) the rise in pressure increases the tension directly, and (2) such distention of the wall also increases the radius, further enhancing the tension If the pressure in a living vessel rises over a long period of time, inherent vital mechanisms will normally cause the connective tissues of the wall to hypertrophy, adapting it to increased tension by increased strength. However, if the rise in tension is more rapid than can be met by the development of hypertrophy, or if the wall is weakened by pathologic processes, stretching of the wall may tend to become progressive Factors distending a vessel increase the tension on its wall, thereby thinning and weakening it while causing a further increase in the radius At a critical point (Fig 2-57, E), this process can lead to ballooning of a segment of the vessel, with formation of an aneurysm or a varicosity (Fig 2-57, F, G, H) Because the tension is greater in an aneurysmal dilatation than in an adjacent segment of the vessel, a tendency to further enlargement of the dilated segment becomes manifest Further stretching of the wall leads to elongation of the vessel If the ends of such a vessel are at fixed distances from each other, such lengthening produces tortuosity. When the tension rises beyond a critical value, the force acting on the vessel is no longer balanced by the resistance or tension of the wall, and rapid stretching and [illegible]

[illegible] ...an the energy of the stream is manifested as *pressure* This is equivalent to saying that the molecules of the fluid beat against the wall with a force equal to the entire pressure head. When flow takes place, some of the pressure head is converted to kinetic energy, and the lateral pressure falls accordingly (*Bernoulli's principle*). Fluid flow is of two general kinds, laminar and turbulent. *Laminar flow* is a motion in which each "filament" of liquid retains its identity and flows smoothly beside its neighbors. It is the type of streamlined motion which curves smoothly around irregularities in its path, rather than setting up whirls and eddies as it moves past. Normally, flow in the arteries and veins is laminar. By contrast, each fluid element in *turbulent flow* moves irregularly with reference to its neighbors, with a considerable loss of energy.

Resistance to Flow. A relationship between driving pressure head and the rate of flow (milliliters per second) may be expressed as resistance When necessary, the resistance of laminar flow through various vascular beds may be effectively compared by use of the arbitrary relationship·

$$Resistance \propto \frac{\text{effective pressure head}}{\text{volume flow}}$$

Numerous formulas in the literature utilize different constants and interrelationships to convert pressure and flow into various units. Sometimes the resistance is expressed in the form:

$$\frac{\text{Dynes/cm}^2}{\text{cm}^3/\text{sec}} = \text{dynes sec cm}^{-5}$$

A ratio is thus obtained which may have value for comparison of the resistances of various beds or in establishing a change in resistance from one test period to another However, the complexity of the cardiovascular system often reduces the value of these attempts at quantitative analysis

Hagen-Poiseuille Flow. The quantity of laminar flow, *Q*, through a uniform tube of circular cross section is directly proportional to the difference in pressure, *P*, between the inlet, *i*, and outlet, *o*, of the tube, i.e., $Q \propto Pi - Po$. Resistance to flow through a tube increases with its length, *L*, thereby reducing flow through it ($Q \propto 1/L$) for a given pressure head. Flow also diminishes as the viscosity, μ, of the fluid is increased ($Q \propto 1/\mu$). This is apparent when one considers that for a given pressure head, more water than molasses will flow through a given pipe The quantity, *Q*, of laminar flow increases according to the fourth power of the radius of the tube ($Q \propto r^4$). This relationship depends on the combined effects of a geometric

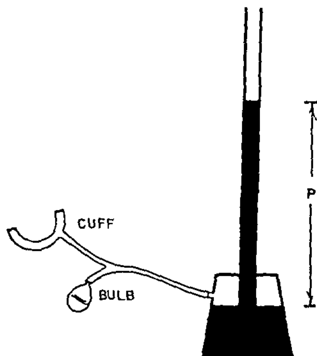


Fig. 2-56. Schema of common blood pressure sphygmomanometer. The cuff is fixed around the arm by suitable wrappings. Air pressure is increased by means of the bulb, causing the mercury (black) to rise to a height which indicates the pressure, *P*, in the cuff.

elevation of the two sites. If the difference in the two levels is measured in centimeters, the pressure difference is obtained in centimeters of blood. The specific gravity of blood is about 1.05, the product of the difference and the specific gravity will then give the pressure in centimeters of water This value may be converted to centimeters of mercury, by dividing the value by the specific gravity of mercury, 13 6.

Pressure Measurement. A *manometer* is a device which balances the pressure in a system against a column of fluid The U-tube manometer used in physiology laboratories registers the pressure acting on one arm by determining the difference between the levels of the two arms of the U tube. The pressure in sphygmomanometers is indicated by the height to which the mercury column rises, the scale being slightly modified to adjust for the small fall in the level of the reservoir as mercury is displaced from it (Fig. 2-56)

A *diaphragm manometer* produces its results because the membrane yields in a consistent manner to the pressure applied to one of its surfaces. The action of membrane manometers may be complex, particularly when pulsating systems are being studied. Such instruments require considerable study before detailed conclusions can be drawn from the tracings obtained. This is because of special properties of the system such as damping characteristics, resonance, compressibility, and others. A *differential manometer* measures the pressure difference between two systems. For example, if the pressure in the left atrium is 30 mm Hg at a time when the pressure in the left ventricle is 10 mm Hg, the differential manometer registers a differential pressure of 20 mm Hg by permitting application of the pressure of one chamber on one side of a membrane while the pressure of the second chamber acts on the other side.

Pressure-Volume Relationships. If fluid is pumped into an empty vein or other vessel, no pressure is generated until the vessel fills and rounds out (indicated at *A* in Fig. 2-57). This may be compared with the process of partially blowing up a paper bag. until the bag is filled, no pressure is present and no tension is developed in the walls. After filling and rounding out, injection of more fluid, while distending the vessel but little, will sharply raise the pressure in it (Fig. 2-57, *B*). A plot of the relation between the volume injected and the pressure which results describes the elastic properties of the vessel (Fig 2-57). If a blood vessel is thin walled and easily distensible, large volumes may be injected without a marked rise

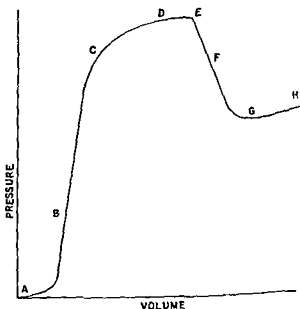


Fig 2-57. Pressure-volume relationships of an elastic tube. Discussed in text.

in pressure (Fig 2-57, *C*, *D*, *E*). If on the other hand the vessel wall is relatively firm, the pressure will rise sharply when even small volumes of fluid are added Pressure generates *tension* in the wall of the vessel by causing it to be stretched (strained). This tension is similar to the strain generated in a wire when a weight is attached to the dependent end In a tube, the tension, *T*, generated in the wall is proportional to the product of the pressure, *P*, multiplied by the radius, *R*, i e , $T \propto PR$. As a consequence of this relationship, injection of fluid into a distended vessel increases the tension in the wall in two ways, since (1) the rise in pressure increases the tension directly, and (2) such distention of the wall also increases the radius, further enhancing the tension If the pressure in a living vessel rises over a long period of time, inherent vital mechanisms will normally cause the connective tissues of the wall to hypertrophy, adapting it to increased tension by increased strength. However, if the rise in tension is more rapid than can be met by the development of hypertrophy, or if the wall is weakened by pathologic processes, stretching of the wall may tend to become progressive Factors distending a vessel increase the tension on its wall, thereby thinning and weakening it while causing a further increase in the radius At a critical point (Fig 2-57, *E*), this process can lead to ballooning of a segment of the vessel, with formation of an aneurysm or a varicosity (Fig 2-57, *F*, *G*, *H*) Because the tension is greater in an aneurysmal dilatation than in an adjacent segment of the vessel, a tendency to further enlargement of the dilated segment becomes manifest Further stretching of the wall leads to elongation of the vessel If the ends of such a vessel are at fixed distances from each other, such lengthening produces tortuosity When the tension rises beyond a critical value, the force acting on the vessel is no longer balanced by the resistance or tension of the wall, and rapid stretching and [illegible]

wh[illegible] [illegible] all the energy of the stream is manifested as *pressure* This is equivalent to saying that the molecules of the fluid beat against the wall with a force equal to the entire pressure head. When flow takes place, some of the pressure head is converted to kinetic energy, and the lateral pressure falls accordingly (*Bernoulli's principle*). *Fluid flow* is of two general kinds. laminar and turbulent. *Laminar flow* is a motion in which each "filament" of liquid retains its identity and flows smoothly beside its neighbors. It is the type of streamlined motion which curves smoothly around irregularities in its path, rather than setting up whirls and eddies as it moves past. Normally, flow in the arteries and veins is laminar. By contrast, each fluid element in *turbulent flow* moves irregularly with reference to its neighbors, with a considerable loss of energy.

Resistance to Flow. A relationship between driving pressure head and the rate of flow (milliliters per second) may be expressed as *resistance*. When necessary, the resistance of laminar flow through various vascular beds may be effectively compared by use of the arbitrary relationship:

$$\text{Resistance} \propto \frac{\text{effective pressure head}}{\text{volume flow}}$$

Numerous formulas in the literature utilize different constants and interrelationships to convert pressure and flow into various units. Sometimes the resistance is expressed in the form:

$$\frac{\text{Dynes/cm}^2}{\text{cm}^3/\text{sec}} = \text{dynes sec cm}^{-5}$$

A ratio is thus obtained which may have value for comparison of the resistances of various beds or in establishing a change in resistance from one test period to another However, the complexity of the cardiovascular system often reduces the value of these attempts at quantitative analysis

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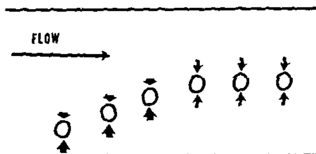


Fig. 2-58. The tendency for migration to the central stream. The parallel lines represent the outer limits of the vessel. Ellipsoids represent red blood cells at various distances from the wall of the vessel Arrows indicate the pressures acting on the surface of each cell. The pressure on the mural aspect is greater than that on the side facing the central streamlines. Flow thereby induces the differential pressures which cause the particles to move to the central streamlines.

factor and a *dynamic* factor, each of which contributes a square function, as indicated below. The cross-sectional area, A, of a pipe increases according to the square of the radius, r^2, thereby accounting for the *geometric* factor affecting laminar flow through pipes ($A \propto r^2$). The special characteristics of laminar flow account for the *dynamic* factor. A red cell in layers of fluid adjacent to the vessel wall moves *relatively* slowly because of the friction between the wall and its boundary fluid The next adjacent layer slides relatively freely on the boundary layer, and cells in this layer move more rapidly The more central laminae slide on those adjacent to them and therefore move even more rapidly. As a result, a red cell in the central laminae, or axis of the tube, will move many times faster than those in layers near the wall. As the pipe increases in radius, the velocity of the central lamina increases rapidly. The velocity of a particular lamina is related to a factor comprising the square of its distance from the wall, because the velocity distribution is parabolic. Since the geometric and the dynamic factors both contribute a square factor to the rate of flow through a vessel, a factor equivalent to the fourth power of the radius, r^4, determines the volume of flow These several factors make up the volume-flow relationship, which is equal to

$$\frac{\left\{\begin{array}{l}\text{Pressure difference between inlet and outlet}\\ \times \text{ radius}^4\end{array}\right\}}{\text{viscosity} \times \text{length of pipe}}$$

Kinetic Energy. During flow, fewer molecules beat against the wall, since many o[f] them are moving forward rather than laterally i e., much of the pressure head is manifeste[d] as kinetic energy (K.E.). As a result, the pressure distending the wall is reduced. As th[e] velocity increases, marked falls in lateral pressure may take place. The K.E utilized in th[e] forward movement of the stream is proportiona[l] to the square of its velocity, i e., $KE \propto V$[…] This conversion of flow energy to pressure energy is easily illustrated by the clinical oscil[…]lometer. This instrument responds to the pul[…]sating volume changes in the segment of ex[…]tremity enclosed by the cuff. The amplitude o[f] pulsations is due to the pulsating force of th[e] blood pressure which distends the elastic ar[…]teries with each pulse wave. If blood flow int[o] the extremity is obstructed by a tourniquet, th[e] amplitude of the pulsation increases, since th[e] energy normally used in flow is now converte[d] to pressure energy.

Skimming. Blood corpuscles tend to mov[e] into the axial stream. This effect also depend[s] on the interrelation between pressure and ve[…]locity. A cell in the stream disturbs the uni[…]form pressure distribution across the tube i[n] such a way that the velocity on the axial sid[e] of the particle is increased and the pressure i[s] accordingly decreased. On the side of the ce[ll] facing the wall, the velocity is decreased an[d] the pressure is increased As a result the highe[r] pressure on the wall side drives the cell int[o] the axial stream (Fig. 2-58) Consequently, th[e] cells tend to be pushed to the central an[d] fastest layers of the stream. These effects ma[y] have physiologic importance by providing [a] more rapid transport for cells than might b[e] indicated by a measurement of the *mean* bloo[d] flow past a point On the basis of this principl[e] branches which come off the main vessel at [a] sharp angle, as in the renal arteries, would ten[d] to skim off a greater proportion of plasma tha[n] would be indicated by hematocrit measure[…]ments of the general venous or arterial bloo[d]

Turbulent Flow. The above discussion con[…]cerns flow when the streamlines are *lamina[r]* However, when a vessel is curved or its inne[r] wall is roughened, and particularly when th[e] velocity is increased to a critical value, th[e] streamlines may become broken into turbulen[t] eddies The viscous forces tend to hold th[e] laminae in their relative positions. At critica[l]

velocities, the surrounding laminae become unbalanced and cause the eccentric layers to push in and disrupt the normal streamlined structure of the central flow pattern. In turbulent flow, a red blood cell tends to fluctuate up and down and from side to side as it moves along, so that its motion differs from the smooth streamlines of laminar flow. A significant portion of the energy of the stream is dissipated in this manner, being no longer available to produce forward flow (Fig 2-59A). The onset of such turbulent flow may significantly reduce the delivery normally achieved by a given pressure head Energy losses due to turbulence can be so important that engineers concerned with maintaining maximal flow at least energy cost try not to exceed the critical velocities at which disruption of the streamlines and turbulence occur Such energy losses due to turbulence may also have importance in cardiology if they increase the work load of an already overburdened heart In other situations, where heat transfer and diffusion of gases or other materials are of prime importance, the induction of turbulence may enhance the rate of transfer between the stream and the surrounding medium. The likelihood of occurrence of turbulence increases as the radius of a vessel enlarges Thus, there is a much greater tendency for turbulence in the aorta than in smaller vessels The likelihood of turbulence is also greater in fluids of low viscosity These relationships are indicated in the *Reynolds number:*

$$\frac{\text{Density} \times \text{velocity} \times \text{radius}}{\text{viscosity}}$$

Flow conditions can thus be characterized by a dimensionless ratio, the Reynolds number, N_r When turbulence develops, vibrations may become evident. This fact has been used to explain the production of murmurs in the heart and arteries The sounds produced by turbulence of this type are generally high pitched, generating frequencies of 1,500 cps or more *High-pitched* murmurs of aortic or mitral insufficiency occasionally have such a turbulent quality However, these whistling sounds differ markedly from the pitch of the coarse sounds heard in stenotic murmurs or over arteries compressed during measurements of the blood pressure As the velocity of the stream increases, more energy is utilized in movement, and less energy is available to act as pressure

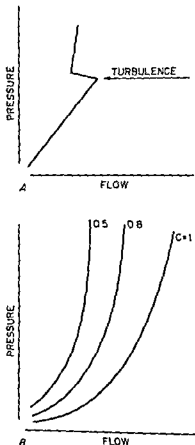


Fig. 2-59 A Effects of turbulence Despite an increase in pressure head, the onset of turbulence and reduced flow at critical velocities is indicated B Effect of pressure on flow through an orifice with various contraction coefficients, C.

on the wall At critical velocities, little or no energy may be available to distend the vessel This effect is seen at constrictions, convergences, or other sites of rapid pressure drop When the velocity becomes excessive, the distending pressure falls below that of the wall pressure and the phenomenon of *lift* (also commonly called *suction*) may become apparent This is similar to the lift produced by the rapid flow of air across the upper surface of an airplane wing

Chatter. At critical velocities, these forces may be sufficient to displace the vessel wall in the direction of the center of the lumen Since the velocity of the axial stream is greater than that of the lamina at the normal vessel wall, the lifting effect is markedly enhanced and the opposite walls of the vessel will move rapidly toward each other, transiently closing the

lumen and obstructing flow. As flow stops, all the energy of the stream becomes manifest as pressure, forcing the walls apart, and flow begins again. As the velocity of the stream then increases, the walls of the channel recurrently snap shut and reopen and the cycle repeats itself Somewhat similar phenomena, which may be called *chatter*, are seen in the flapping of a flag in the breeze, and in the vibration of the reeds of musical instruments and of the vocal cords. *Low-pitched murmurs* may result from similar patterns of flow through stenosed valves or through the partially compressed brachial artery during indirect blood pressure measurement.

Cavitation. Cavitation is a "boiling" process which occurs when the velocity increases so much that the local pressure falls to levels approaching the vaporization point of the fluid. When the velocity of blood is very high, as may occur at a stenotic aortic or pulmonary valve, the local pressure may fall to the vaporization pressure of the blood water (47 mm Hg) and the partial pressure of the blood gases Bubbles will then form containing water vapor and the dissolved gases, oxygen, carbon dioxide, and nitrogen These bubbles collapse as they move away from the site of excessive velocity to regions of lower velocity and higher pressure While bubbles can form instantaneously, a longer period is required for their re-solution in the blood Cavitation may thus potentially produce tiny hematogenous bubbles which may act as ephemeral emboli. Cavitation may also produce corrosion of the surface at sites of bubble collapse, if this action occurs at a valve, trauma to a leaflet may result

Flow through an Orifice. The quantity, Q, of flow through an orifice is proportional to the *cross-sectional area, A, of the orifice, i e, $Q \propto A$.* Passing through an orifice, the stream of fluid tends to contract, reducing the effective area of the orifice to less than its actual size. A constant, c, with a value less than 1 is therefore introduced into the proportionality $Q \propto cA$. If the lips of the opening are rough or of irregular or elliptical (fish-mouth) shape, flow is further reduced. These variants require the addition of other modifying constants, c, each having a value less than 1, and the formula becomes modified to read, $Q \propto c_1c_2A$. The greater the number of constants in attendance, the less will be the flow through a given orifice. Usually the several constants are collected into a single value, C, and the statement is given simply as $Q \propto CA$. The pressure head above the orifice provides the force impelling fluid through it. Very low pressures are sufficient to produce a very considerable flow through an orifice, as the pressure is increased, flow does not increase in a linear fashion (Fig 2-59B). Instead the quantity of flow is related to the square root of the pressure head, $Q \propto \sqrt{P}$. The combination of the geometric factors related to area, CA, and the dynamic factor due to pressure, $\sqrt{P}$, gives the general rule for flow through an orifice: $Q \propto CA\sqrt{P}$. Interpretation of this relationship gives interesting patterns, some of which have been applied in attempts to estimate the size of orifices of stenotic mitral or aortic valves. For example, a pressure *of 1 mm Hg will produce a given flow through* an orifice, an increase of the pressure to 10 mm Hg increases the flow not by ten times, but by only three times ($\sqrt{10} = 3.1$) An increase in available pressure to *100 mm Hg will* produce only ten times as much flow as the pressure of 1 mm Hg *It can be seen that an orifice permits a relatively free flow at low pressure but that the flow volume does not keep pace with a rise in effective pressure.*

Secondary Flow in Curved Tubes. Flow through an arched pathway like that of the aorta generates centrifugal forces which produce an internal pattern of *secondary flow* The axial stream, having the most rapidly moving components, tends to move in a straight line and is displaced to the outer wall of an arching vessel The slower lateral laminae are pushed to the inner curvature of the channel In consequence a secondary flow is set up in which *two separate streams* move through the arch giving rise to a complex pattern of spiral flow.

Jet. A jet is produced as high pressure extrudes fluid through a constriction. Such a jet tends to strike a small area of a wall with considerable force, proportional to the square of the velocity, $F \propto V^2$. Thus, a doubling of the jet velocity increases the force beating on the wall by a factor of four If the velocity were increased ten times, the force of the jet would be amplified a hundredfold The destructive potential of jets may thus be appreciated

Water Hammer. Vascular pressure waves

and sounds are *sometimes* attributed to the phenomenon of *water hammer* The sudden closing of a valve or faucet obstructs a column of fluid whose momentum nevertheless causes it to continue to move forward A transitory surge of high pressure is thereby generated and, if the tube is relatively rigid (as in household water systems), elastic rebound of the wall quickly returns the pipe to its original shape, ejecting the excess fluid and generating a knock and a pressure wave which are transmitted away from the faucet at the speed of sound This pressure wave may be reflected from some distant point to the closed faucet, causing a second pressure build-up and a second knock Sudden closure of a valve may thus generate a series of knocks (water hammer) before its force is dissipated. Even slight damping of a tubular system eliminates water-hammer shocks This is accomplished commonly by inclusion of a small air cushion near the faucet of a water pipe system. The likelihood that water-hammer effects can be produced in the normal cardiovascular system is precluded by the rubber-like distensibility of the arterial tree The possibility remains that water-hammer phenomena may occur in patients with severe diffuse arteriosclerosis

I

The dynamic phenomena of the large vessels and the mechanism of poststenotic dilatation

EMILE F. HOLMAN

"The physical principles involved in the hydrodynamics of the circulation are of great complexity, and are for the most part as yet incapable of strict mathematical treatment. Nevertheless, certain elementary principles of hydrodynamics help towards a partial elucidation of the problems involved." Thus wrote Evans (1952) in *The Principles of Human Physiology* In the same year, Wyssling wrote: "The whole problem of pressure-flow relation of blood needs much further investigation." Since these statements were published, the application of hydrodynamic principles to the circulation of blood has provided acceptable explanations for certain circulatory phenomena which have long intrigued both physiologists and surgeons.

In the circulation of blood, there occurs occasionally a partial constriction in the stream diameter which is accompanied by dilatation distal to the site of narrowing Paradoxically, this dilatation does not occur proximal to the obstruction, as one might expect, but *distal* to it. Conspicuous examples are the dilatation of the ascending aorta distal to a congenital subaortic stenosis, not infrequently mistaken for an aneurysm (Fig. 2-60A, B); the dilatation distal to congenital stenosis of the pulmonic valve, which may also assume aneurysmal proportions (Fig. 2-60C, D); the frequent, though not invariable, dilatation of the thoracic aorta beyond a congenital coarctation (Fig. 2-61A); and the occasional aneurysmal dilatation of the subclavian artery just distal to its compression between the scalenus anticus and an anomalous cervical rib (Law) (Fig 2-61B). Halsted once placed on record a strikingly unique example of *acquired* poststenotic dilatation.

Experimentally, poststenotic dilatation can be produced almost at will and, under certain circumstances, within a relatively short time Puppies belonging to the same litter were subjected to stenosis of the thoracic aorta by throwing a ligature about the vessel which did not immediately constrict it, but which limited its diameter as the puppy grew to maturity. Dilatation distal to the ligation occurred in each instance, and was well advanced by the eighty-sixth day (Fig 2-61C)

In a 78-day-old pup, two constricting ligatures were applied to the thoracic aorta, 4 cm apart Pressure proximal to the first constriction in this refrigerated animal was found to be 60 mm Hg Beyond this constriction and before applying the second constriction, a pressure of 40 mm Hg was recorded. After applying the second ligature, the pressure between the two constrictions was 50 mm Hg, and beyond the second, 30 mm Hg. Six and one-half months later, when the animal was killed, a marked dilatation was present beyond the first

ligature (Fig 2-62A) and a definite, though milder, dilatation was observed distal to the second The latter is explained by the low pressure proximal to the second constriction as compared with the higher pressure proximal to the first constriction

Of particular significance were the behavior and fate of a concentrated solution of methylene blue injected into the flowing stream When injected *beyond* the constriction, the dye disappeared without delay into the fast-flowing distal stream However, when the dye was injected *proximal* to the stenosis, there was noted just distal to the constriction a definite delay in its progress downstream It appeared to be involved in turbulent eddies before it hesitatingly resumed its forward flow (Fig. 2-62B). It was even seen to reverse its direction, momentarily, and to flow backwards toward the stenosis. The site of delay and of turbulence

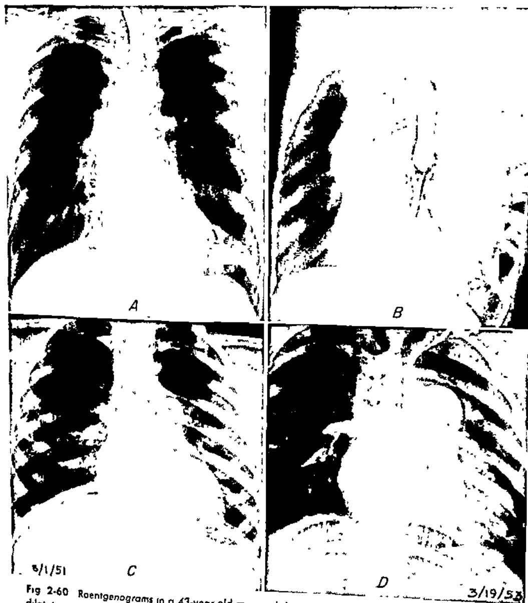


Fig 2-60 Roentgenograms in a 43-year-old man with heart disease since infancy show aneurysmal dilatation of the ascending aorta distal to a congenital subaortic stenosis A, P–A, B, LAD, C, marked prominence of the pulmonary artery to left of midline, D, angiogram confirms the presence of a marked dilatation of the pulmonary artery beyond a pulmonic valvular stenosis, which was incised and dilated at a subsequent operation

I

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impacts of alternating high and low pressures which strike repeatedly and relentlessly against the elastic wall, resulting eventually in its distention. These impacts also cause the vessel wall to vibrate, the vibrations being recognizable as a palpable thrill and an audible bruit. The site of conversion of high K E into high lateral pressure, the location of maximal clash of streams, the zone of greatest turbulence, and therefore also the site of greatest thrill and bruit, *all coincide with the location of maximal dilatation*, which usually lies 1 to 3 cm beyond the constriction, depending upon the pressure and velocity of flow

A third factor concerned in the dilatation beyond a stenosis is the *lowered velocity*, due to the widening of the stream diameter resulting from the operation of the first two factors. According to the Bernoulli principle, this lowered velocity will of itself increase lateral pressure, *thus providing for even greater dilatation* In a pulsating stream, the first two factors recur repeatedly with each systole, and set the stage for the third factor to act, also in repetitive manner. The inevitable result of these three recurring stresses in a pulsating stream operating in a localized segment of an elastic, distensible vessel is a vicious circle greater lateral pressure → greater widening of the stream diameter → lessened velocity of flow → greater lateral pressure, etc

Under certain conditions, dilatation is insidiously progressive once these hydraulic forces are brought into play. Evidence suggests, however, that there is a maximal degree of dilatation for each set of conditions under which it occurs, that dilatation varies in degree with the pressure and velocity with which blood is ejected from the stenotic channel, and that there is a critical level of pressure and velocity below which dilatation does not occur. The element of time is most important, dilatation appearing only after the hydrodynamic stresses have operated for a sufficient time.

An important factor determining both the extent and rapidity of development of dilatation is represented by the structural qualities of the vessel wall, with particular reference to its rigidity and distensibility When the resistance to further dilatation inherent in the structure of the vessel equals the hydrodynamic forces generated by the stenosis, no further dilatation will occur. Manifestly, also, dilatation will continue as long as the hydraulic forces produced by the stenosis exceed the resistance to dilatation imposed by the structural characteristics.

Other determining factors are the degree of stenosis, the compressibility or incompressibility of the tissues and structures surrounding the vessel, the viscosity of the circulating fluid, and the diameter of the vessel in relation to the pressure and velocity of flow in it. It appears that unless the lumen is reduced to one-third or one-fourth its original diameter by the stenosis, turbulence of flow will be minimal, as disclosed by only a mild thrill and bruit, and dilatation will be minor, long delayed, or completely absent. Moreover, greater dilatation will occur in the unsupported thoracic and abdominal vessels in contrast with a more limited dilatation in the muscle- and fascia-surrounded vessels of an extremity.

Other clinical conditions prevent entirely or modify significantly the development of poststenotic dilatation Most importantly, the vol-

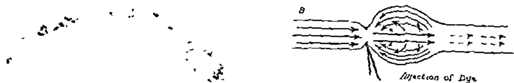


Fig 2-62 A Two constrictions 4 cm apart in the thoracic aorta of a pup both produced poststenotic dilatation in 6 months' time, the dilatation distal to the first constriction was more pronounced because of the higher arterial pressure proximal to it Photograph shows the preserved specimen—in life the pulsating vessel showed even greater poststenotic dilatation beyond each constriction B, When dye is injected proximal to a constriction, remarkable eddies of turbulent and reversed flow are noted just distal to the stenosis where the rapidly ejected stream strikes the more slowly flowing distal stream, and where high kinetic energy is transformed into high potential energy or lateral pressure

of flow was identical with the site of dilatation, as well as with the location of a palpable *thrill* and audible *bruit*.

It is suggested that this dilatation results from the operation of certain hydrodynamic principles that govern the pulsating flow of blood through an expansile elastic tube. During diastole, there occurs a momentary retardation in flow, which is accentuated just beyond a stenosis. During systole, there emerges from the narrow stenotic channel a stream of blood at a greatly increased velocity as compared with the velocity in the broader channel either proximal or distal to the stenosis.

Mathematically, the *velocity of flow, other factors remaining the same, is inversely proportional to the square of the radius*. Obviously, if a tube 18 mm in diameter is reduced abruptly for a short distance to a diameter of 6 mm, the velocity through the constriction is increased nine times. Conversely, if a tube 6 mm in diameter is increased to a diameter of 18 mm, the velocity will be reduced abruptly to one-ninth its previous rate. In systole, therefore, *the rapidly ejected, narrowed stream runs* head on, as it were, into the more slowly flowing, relatively stagnant, and wider poststenotic stream, resulting in a sudden arrest in its forward flow. *The conversion of the high kinetic energy* (K.E.) of the swiftly moving stream *into high potential energy* or *lateral pressure* is the first factor in the development of poststenotic dilatation.

Secondly, the clash of two streams of differing velocities produces *eddies* of turbulent and reversed flow, accompanied by shocks or

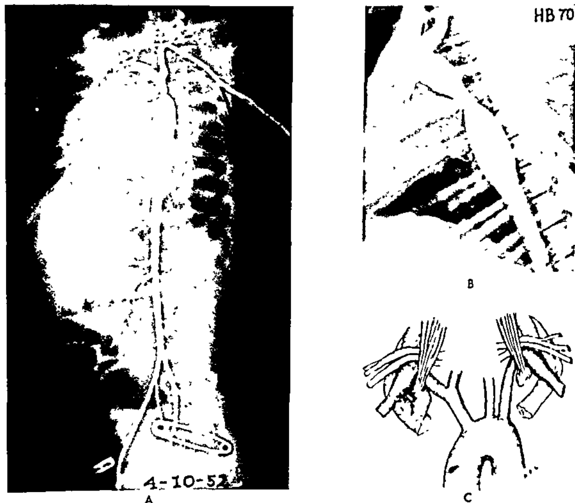


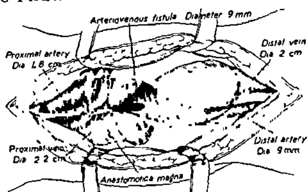
Fig 2-61. A. Aortogram of a 5-month-old child shows characteristic dilatation beyond a coarctation of the thoracic aorta. B Typical bilateral poststenotic dilatation accompanying compression of subclavian artery by scalenus anticus at point of attachment to abnormal cervical ribs (Case of Law. *Lancet*. 1914.) C. Aortogram from a puppy shows *well-developed* poststenotic dilatation 86 days after subjecting the animal to constriction of the thoracic aorta.

are likewise diffusely distributed in diminishing degree, resulting in a tapering dilatation of the vessel wall.

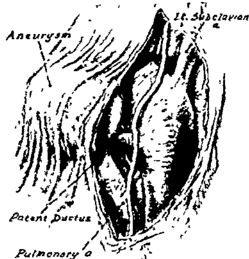
The absence of dilatation *proximal* to the constriction is dependent upon the fact that the pressures here are evenly and uniformly distributed against the limiting vessel wall, and as there is no arrest in the forward flow, there is no conversion of high K.E. into high lateral pressure. General pressure proximal to the stenosis may be higher than the pressure distal to it, but it is a relatively uniform level of pulsatile pressure, evenly distributed throughout and not subject to the rapidly oscillating variations of high and low pressure such as occur in the turbulent flow produced by the clash of streams distal to the stenosis. As a result of this uniform distribution of pressure proximal to the stenosis, uniform expansion of the vessel occurs with each pulsation.

These clinical and experimental observations carry wide implications. They strongly suggest, for example, that the initiating factor in the development of an aneurysm may be a stenosis of the arterial lumen imposed by a segmental atherosclerosis or by a localized fibrosis, through which a narrowed stream flows with increased velocity into a normally distensible and wider distal segment or into a segment weakened by disease, thus setting the stage for the play of hydraulic forces effective in producing a localized dilatation beyond a stenosis.

Many observers have noted the appearance of aneurysms just beyond the creases of the body, in the groin, just beyond compression by the inguinal ligament, in the popliteal artery, just back of the knee, where constant flexion and extension may traumatize the vessel with localized fibrosis or production of atherosclerosis, narrowing of the stream, and the unleashing of hydrodynamic stresses distad to the stenosis. The potential dilating effects of these hydrodynamic stresses produced by a real or relative stenosis deserve our interest. They help to explain the destruction of bone and of surrounding structures that occasionally accompanies the development of a thoracic aneurysm. They explain the aneurysmal dilatation of the vein usually seen beyond an arteriovenous fistula where the arterial stream under high pressure and high velocity is ejected into the widened bed of the vein through a relatively narrow fistulous opening, simulating a stenosis (Fig. 2-64A). Here the peripherally directed arterial stream clashes head on throughout the cardiac cycle against the returning venous stream, producing a marked turbulence of flow and causing a continuous thrill and a bruit. The hydrodynamic forces unleashed distal to the relatively stenosed fistula invariably produce a fusiform dilatation of the



A



B

Fig. 2-64. A. In arteriovenous fistula, marked aneurysmal dilatation of vein occurs almost invariably distal to the fistula, which acts as the site of a relative stenosis through which arterial blood is ejected under high pressure and high velocity into the broad stream of the vein. B. Marked aneurysmal dilatation of pulmonary artery just beyond the site where a narrow patent ductus ejects blood under high pressure and high velocity into the pulmonary artery of lower pressure and wider stream.

ume of blood forced through the constricted channel and, therefore, the velocity of flow with which the blood is ejected from the stenosis may be greatly altered by conditions just proximal to the stenosis: *well-developed collateral channels,* such as greatly dilated subclavian arteries, may reduce the volume flow through an aortic coarctation, and postconstriction dilatation may not occur or may be limited in degree.

An *open ductus* located just proximal to a coarctation may prevent dilatation beyond the constriction by draining away a large volume of blood into the lower resistance bed of the pulmonary artery, thus reducing the pressure and velocity of flow through the coarctation (Fig. 2-63A). An *interventricular septal defect* and an *overriding aorta,* as in the tetralogy of Fallot, may prevent dilatation of the pulmonary artery by providing a large runoff or deflection of blood away from the stenosis, thus reducing markedly the pressure and velocity of flow through the narrowed segment of the pulmonary artery (Fig 2-63B)

Rarely, dilatation may develop in the small "ampulla" lying just between a sharply localized *infundibular stenosis* and the normal pulmonic valve (Fig. 2-63C). If the stenosis is limited to the pulmonic valve itself, *poststenotic dilatation of the pulmonary artery* of varying degree may occur depending upon the extent of the diversion of blood flow through the interventricular septal defect into the overriding aorta. If this deflection of blood is small, the dilatation of the pulmonary artery may be quite marked. If the deflection is great, the dilatation will be mild or absent.

A supremely important factor involved in the dilating effect of these minute but relentless hydraulic stresses imposed upon a vessel wall by a stenosis in a pulsating stream is the extraordinary phenomenon of *structural fatigue,* long known for its peculiarly destructive and critically important qualities in the physical world of metals. Unevenly distributed in the zone of turbulent flow are alternating waves of high and low pressure resulting in impacts or shocks of high local stress against minute areas of the limiting vessel wall. These frequently repeated, inexorably recurring impacts of high stress against the vessel wall produce structural fatigue and eventually distention of the yielding elastic wall. As the points of stress beyond the stenosis vary in position and in intensity from moment to moment and are diffusely distributed in diminishing degree throughout the zone of increased lateral pressure, the points of strain and structural fatigue

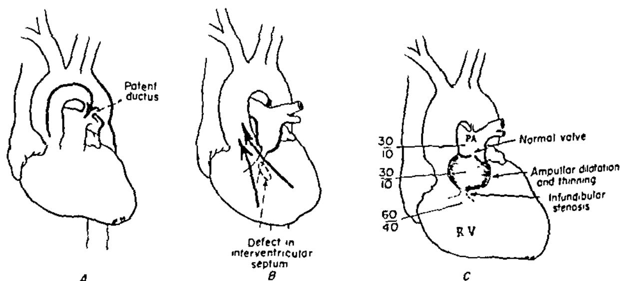


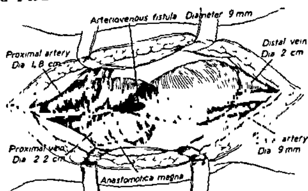
Fig. 2-63. Certain conditions prevent dilatation beyond a stenosis A A wide open ductus proximal to a coarctation effectively diverts sufficient blood away from a coarctation to prevent the usual dilatation beyond the coarctation B An interventricular septal defect and an overriding aorta provide diversion of blood away from the pulmonary artery, thus diminishing pressure and velocity of flow through the accompanying infundibular stenosis (tetralogy of Fallot) C. Rarely, dilatation occurs in the ampulla between a sharply localized infundibular stenosis and a normal pulmonic valve.

are likewise diffusely distributed in diminishing degree, resulting in a tapering dilatation of the vessel wall

The absence of dilatation *proximal* to the constriction is dependent upon the fact that the pressures here are evenly and uniformly distributed against the limiting vessel wall, and as there is no arrest in the forward flow, there is no conversion of high K.E into high lateral pressure General pressure proximal to the stenosis may be higher than the pressure distal to it, but it is a relatively uniform level of pulsatile pressure, evenly distributed throughout and not subject to the rapidly oscillating variations of high and low pressure such as occur in the turbulent flow produced by the clash of streams distal to the stenosis As a result of this uniform distribution of pressure proximal to the stenosis, uniform expansion of the vessel occurs with each pulsation

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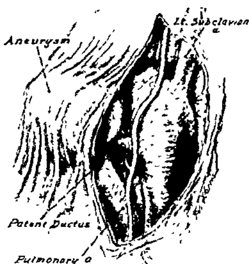


Fig 2-64 A In arteriovenous fistula, marked aneurysmal dilatation of vein occurs almost invariably distal to the fistula, which acts as the site of a relative stenosis through which arterial blood is ejected under high pressure and high velocity into the broad stream of the vein. B Marked aneurysmal dilatation of pulmonary artery just beyond the site where a narrow patent ductus ejects blood under high pressure and high velocity into the pulmonary artery of lower pressure and wider stream

vein, which either is slowly progressive or may reach a maximal degree and then remain stationary, depending on conditions at the site of the fistula.

The occasional aneurysmal dilatation of the pulmonary artery (Fig. 2-64B) in the presence of a patent ductus may also be ascribed to hydraulic forces operating when the arterial stream, *under high pressure and high velocity*, is ejected from the narrow ductus into the pulmonary artery, which has a lower pressure and a wider diameter. Here again a turbulent flow is produced throughout the cardiac cycle, resulting in a continuous thrill and bruit.

It is highly probable also that the sudden cerebral hemorrhage attributed to the rupture of a small aneurysmal dilatation, or *"berry" aneurysm*, of the cerebral vessels has its inception in a precipitate increase of the hydrodynamic stresses within the aneurysm which accompany the heightened pressure and increased velocity of flow incident to emotional stress or physical exertion Likewise, sudden death from rupture of a thoracic or abdominal aneurysm may be ascribed to the great augmentation within the aneurysm, distal to a relative stenosis, of the hydrodynamic forces that accompany the heightened arterial pressure and increased velocity of flow incident to physical or emotional stress.

These and other similar phenomena in the human vascular system may find their proper *explanation in the application of hydrodynamic* laws that govern the pulsatile flow of fluid through an elastic vessel subjected to real or relative narrowing by congenital abnormalities, degenerative processes, or accidental injuries They give warning of the need to employ in the vascular surgery of children methods of end-to-end anastomosis that permit growth at the site of union as the child grows, thus avoiding future stenosis. They illustrate also the necessity of applying methods of suture in vascular surgery that prevent or minimize the development of constriction at the site of anastomosis either by puckering at the time of operation, or by *cicatricial circular contracture* as healing progresses.

17

Physiology of the small vessels

The Control of the Small Blood Vessels

BJÖRN FOLKOW

Contractility of the Capillaries

HANS ELIAS

Vasomotion of the Capillaries

B. W. ZWEIFACH

THE CONTROL OF THE SMALL BLOOD VESSELS

Though morphologically somewhat vague, the term *small blood vessels* is functionally justified as it covers a part of the vascular tree in *which* are important control mechanisms for the cardiovascular function. From a functional point of view, the small blood vessels may be divided into (1) resistance vessels, (2) capacity vessels, (3) shunt vessels, (4) sphincter vessels, and (5) exchange vessels

Resistance Vessels The resistance vessels cannot be directly identified with specific morphologic sections of a vascular bed. Thus, although the arteriolar section offers the main resistance to flow, the functional expression *resistance vessels* includes also capillaries and smaller veins, as they, too, contribute significantly to the resistance (Green, 1950a).

Capacity Vessels. Although the veins contain a major portion of the blood, changes of tone of the small vessels as a unit contribute greatly to the dynamic reservoir function of the vascular bed, as these vessels may contain up to 30 per cent of the blood volume (Green, 1950) As yet knowledge of the control of the capacity function of the vascular bed is very limited

Shunt Vessels. The shunt vessels allow the blood to bypass groups of capillaries These vessels have a characteristic morphology, and a number of more or less well-differentiated arteriovenous anastomoses have been described in various tissues (Grant and Bland, 1931, Clark and Clark, 1934, Clara, 1939, Boyd, 1952; Walker, 1952). With the exception of the arteriovenous anastomoses of the skin, however, their exact significance is largely unknown, and they may have widely different and specific functions in different regions. Thus, recent studies indicate that the much-debated renal shunts, whose existence has been seriously questioned (Smith, 1951. Folkow, 1955), may form a part of a highly specialized blood flow arrangement leading to a partial separation of plasma and cells at the arterial branching (Pappenheimer and Kinter, 1956): the "cell fraction" would flow through the shunt vessels and meet the "plasma fraction" on the venous side of the renal vascular bed Whether [illegible]

[illegible] differences are also seen concerning the responsiveness of the shunt vessels to constrictor substances While the cutaneous anastomoses are highly sensitive to epinephrine (Folkow, 1955), those of the gastric mucosa seem to be only little influenced by this hormone (Walker, 1952)

Sphincter Vessels. Marked variations of the surface available for exchange between blood and tissue can be induced by constrictions of the precapillary sphincter regions (Krogh,

vein, which either is slowly progressive or may reach a maximal degree and then remain stationary, depending on conditions at the site of the fistula.

The occasional aneurysmal dilatation of the pulmonary artery (Fig. 2-64B) in the presence of a patent ductus may also be ascribed to hydraulic forces operating when the arterial stream, under high pressure and high velocity, is ejected from the narrow ductus into the pulmonary artery, which has a lower pressure and a wider diameter. Here again a turbulent flow is produced throughout the cardiac cycle, resulting in a continuous thrill and bruit.

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These and other similar phenomena in the human vascular system may find their proper explanation in the application of hydrodynamic laws that govern the pulsatile flow of fluid through an elastic vessel subjected to real or relative narrowing by congenital abnormalities, degenerative processes, or accidental injuries. They give warning of the need to employ in the vascular surgery of children methods of end-to-end anastomosis that permit growth at the site of union as the child grows, thus avoiding future stenosis. They illustrate also the necessity of applying methods of suture in vascular surgery that prevent or minimize the development of constriction at the site of anastomosis either by puckering at the time of operation, or by cicatricial circular contracture as healing progresses.

muscles, are probably due to the nature of the receptor groups, specific for different excitatory and inhibitory substances These concepts are of prime importance for understanding the neurohumoral control of the small vessels (Furchgott, 1955).

Estimation of the Tone of the Small Blood Vessels Under most circumstances, the blood vessels maintain a certain *tone*, i e, their smooth muscle cells are in a state of continuous activity. This tone creates a "blood flow reserve" for the tissues, which can be utilized to the extent needed by a locally controlled, graded decrease of smooth muscle activity (see below). When pressure, blood viscosity, and length of the vessel system are constant, the resistance to flow is inversely correlated to the fourth power of the internal radius This, in turn, depends upon the average length of the contractile elements of the wall Therefore, the average degree of contraction of the smooth muscle cells of a given vascular bed can be estimated within reasonable limits by relating the actual resistance to flow to that observed during maximal dilatation; this can be looked upon as a morphologically determined "base line" It should be stressed, however, that the correlation between internal radius and variations in length of the contractile elements is not always the same It can be deduced, for example, that a given contraction will reduce the lumen considerably more if the vascular wall is thicker, or, in other words, an increased wall-to-lumen ratio will *in itself* "potentiate" the vasoconstrictor effect Therefore, in case of diffuse wall hypertrophy (as in chronic hypertension), the degree of vascular tone can hardly any longer be evaluated by comparing the resistance to flow to that of a normal vascular bed (Folkow, 1956b) This reasoning also applies to different sections of the same vascular bed, and smooth muscle shortening can be expected to reduce the lumen of an arteriole more than that of a venule with a relatively thin wall Therefore, the tone of limited sections of a vascular bed can be judged only from direct measurements of diameter changes It should be stressed, however, that such direct measurements are significant only if the regional intravascular pressure is kept unchanged If this pressure is allowed to vary, it becomes impossible to differentiate between active contractions and elastic changes of the lumen due to variations in pressure. This fact calls for a great degree of caution when the control of the smallest vessels is studied directly under the microscope.

Regional Differences in Basal Vascular Tone. Early investigators believed that vascular tone depended primarily on the activity of constrictor nerve fibers and that this varied greatly in different vascular beds. The tonic constriction observed after vasomotor fiber block was often assumed to depend upon vasoconstrictor agents in the blood. It is now known that, at least in the case of cerebral and coronary vessels, blood flow is hardly increased by constrictor fiber block, even though, judging by the dilator effects of increased tissue activity, the vascular tone of these vessels is considerable (Schmidt, 1950, Gregg, 1950). In skeletal muscles, after eliminating the influence of the vasoconstrictor fibers, the blood flow can be increased as much as five to six times (Barcroft et al, 1943), indicating that muscle also possesses marked basal vascular tone. On the other hand, the result of acute denervation of the arteriovenous anastomoses of the skin indicates that under such circumstances, they already are almost maximally dilated (Folkow, 1955) Nevertheless, in general, these vessels seem to be more sensitive to constrictor agents released into the blood stream than the vessels of the skeletal muscles. Thus, independent of regional sensitivity to constrictor agents, different regions show great differences in basal vascular tone, indicating that this tone is not primarily dependent upon circulating constrictor agents, further, there is evidence that the blood concentration of such agents is insignificant under resting conditions (Lofving and Mellander, 1956).

Myogenic Activity in the Small Vessels. From the observations above, it is obvious that basal (residual) vascular tone *must* be ascribed to some local mechanism and may be most easily explained by assuming an automaticity of the contractile elements, such as that observed in the smooth muscles of intestine and ureters (Bozler, 1948; Bulbring, 1955) Isolated arteries show "spontaneous" activity, which is unaffected by neurologic blocking agents (Furchgott, 1955). It is likely that the "vasomotion" of the small vessels (which is very strong, for example, in the venules of the bat's wing) is basically due to automaticity,

1929, Martin et al., 1932; Bucherl and Schwab, 1951–1952). These constrictions are often strong enough to block the lumen and effectively exclude the corresponding capillaries from diffusion exchange. The control of filtration on exchanges across the capillary walls, so important for the regulation of the blood volume, is also dependent upon the tone in these and adjacent vascular sections, which affects both the capillary pressure and the size of the filtration surface. Further, the time available for capillary exchange is also dependent on the tone of the sphincter regions. In resting conditions, the blood flows through a capillary in about 0.5 to 1 sec. During tissue activity, the dilatation of resistance vessels must be accompanied by the opening of previously closed sphincters, so that the increased flow can be directed through a proportionally increased number of capillaries. Otherwise, a reasonable exchange equilibrium between blood and tissue might not always be maintained. It is known, for instance, that in the lungs the alveolar-arterial P_{O_2} difference is raised when the cardiac output increases markedly. This may be due, at least partly, to the shorter passage time of the blood through the pulmonary capillaries, even though more capillaries are open (Roughton, 1945).

Exchange Vessels. For all practical purposes, the exchange between the circulating blood and the tissues—the ultimate purpose of the cardiovascular system—takes place within the true capillaries, with their immense porous surface and thin walls (Pappenheimer, 1953), however, the endothelium of other sections of the small vessels is not entirely impermeable. For example, the arteriolar endothelium contains pores which may allow vasoactive substances to pass directly from blood to smooth muscle cells of the arterioles themselves. Lipid-soluble factors, like oxygen and carbon dioxide, which can diffuse through an endothelial surface (Pappenheimer, 1953), *will be able to reach* the contractile elements of these vessels directly from the blood stream and not only by way of true capillaries and tissue spaces.

Flow Capacity in Different Vascular Regions. Under physiologic conditions, the blood flow through a tissue area is determined only to a limited extent by viscosity or pressure changes as both are kept fairly constant by appropriate regulatory mechanisms. Therefore, changes in blood flow depend primarily upon changes in vascular resistance. For any given pressure and blood viscosity, a structural upper limit of flow is determined by the diameter, the length, and the total number of the small vessels when their contractile elements are *completely* relaxed. There are reasons to believe that this maximal blood flow capacity of a tissue is correlated primarily to its maximal nutritional needs. In some tissues, however, the vessels also serve other functions. Thus, in the skin, blood flow is engaged in the regulation of heat loss while the *renal* blood constitutes the material from which the primary urine is formed. Therefore, the maximal blood of these tissues is far in excess of their metabolic needs.

The Contractile Elements. Contractile elements are needed in the walls of the small vessels in order to control resistance, capacity, shunt and sphincter functions, and to adapt regional flow to current needs. Their smooth muscle cells form circular layers, considerably thicker in the arterial than in the venous section and becoming more discontinuous towards the true capillaries. The latter lack smooth muscle elements, with the exception of isolated sphincters at the ends (Fulton and Lutz, 1941–1942, Chambers and Zweifach, 1946). In some areas, such as the mesoappendix of the rat, "arteriovenous capillaries" have been described, with muscle elements present throughout their length (Chambers and Zweifach, 1946), but *such an arrangement seems to be the exception rather than the rule*. It has been debated whether the capillary endothelium is able to contract actively. Such a view should be accepted only if direct or indirect participation of muscle elements could be excluded beyond doubt, and most recent investigators are of the opinion that the endothelial cells of mammals do *not* exhibit a true contractility. Capillary narrowing, caused by passive elastic recoil when the intracapillary pressure is lowered by sphincter contraction, or *due to endothelial* swelling after damage to the wall, cannot be considered active constrictions.

The mechanisms responsible for the energy supply and the contraction process of the vascular smooth muscle cells are probably of the same nature as those of other types of smooth muscle. The opposite reactions to drugs frequently observed in different types of smooth muscles, such as vascular and intestinal smooth

Under resting conditions, the small blood vessels (with some possible exceptions such as renal vessels, Smith, 1951) are continuously exposed to a constrictor fiber discharge of about one to two impulses per second, which is controlled predominantly by the medullary vasomotor center. No vasodilator fibers participate in this tonic control of the small vessels (Folkow, 1955). The constrictor control of the cutaneous vessels, especially of the shunts, is primarily governed by the hypothalamic heat-loss center, and, therefore, the discharge of these fibers depends predominantly upon the level of heat exchange (Hensel, 1952)

In many regions of great importance for the total peripheral resistance, such as the splanchnic area, the kidneys, the skeletal muscles, and the skin, the effect of even moderate changes in the rate of discharge of nerve impulses is considerable The medullary vasomotor center can therefore cause remarkable changes in peripheral resistance with relatively small *changes of its* activity. The pulmonary resistance vessels are comparatively little affected by the constrictor fibers (Daly et al, 1952), and there seems in fact to be little need for such a control. The constrictor control of the sphincter and capacity vessels of the lungs should then be far *more important but is insufficiently* known (Folkow, 1955, Duke, 1956)

Dilator Fibers. In some regions, where the basal vascular tone is so pronounced that the inhibition of constrictor tone *does not* result in maximal dilatation, the small vessels are controlled also by specific vasodilator fibers. *Cholinergic dilator fibers of sympathetic origin* are distributed to the vessels of the skeletal muscles (Uvnas, 1954) The fact that these fibers may induce maximal dilatation indicates *that not* only the arteriolar section of the resistance vessels is affected but probably also the sphincter regions and the small veins In other words, these dilator fibers may increase blood flow and also spread this flow over a bigger capillary surface, also, concomitantly, the volume of blood in the muscle may increase somewhat. The central connections of these fibers suggests that they may be able to secure an increased blood flow to the muscles in "emergencies" and possibly also in normal muscular work

Parasympathetic cholinergic vasodilator fibers seem to be distributed to some specialized tissues, such as the salivary glands, the tongue, and certain parts of the genital organs (Folkow, 1956a). These fibers induce a decrease of the resistance to flow, and their main function may be that of adapting the regional blood flow to the degree of tissue activity.

A third type of dilator fibers, distributed primarily to the vessels of the skin and mucous membranes, are the so-called dorsal root dilator fibers They have a different functional significance and probably are identical with the well-known axon reflex of the pain fibers, and are thus independent of central control. These fibers, affecting primarily the smaller arterioles and sphincters, cause regional dilatation when noxious stimuli affect superficial tissues. This local dilator response is involved in the *triple response of Lewis* and favors the processes of defense and repair in the damaged tissue area The transmitter substance is not identified but seems to be related to ATP.

Local Nerve Plexus. It has been suggested that the small vessels are also controlled by local autonomous nervous mechanisms. Histologic studies do not support such a theory, even though certain indirect pharmacologic observations suggest the existence of interconnections between muscle cells (Folkow, 1955, Furchgott, 1955) The nature of these connections is uncertain at the present time

SPECIFIC VASOACTIVE AGENTS IN THE BLOOD STREAM

Several substances of interest for the control of the small vessels may be released into the blood stream The adrenal medulla contains cells secreting both epinephrine and norepinephrine in proportions which vary from species to species and which seem to be under a selective nervous control (Folkow, 1955). In man, the adrenal medulla seems to secrete principally epinephrine (Hokfelt, 1951; von Euler, 1956) Epinephrine differs from norepinephrine because it dilates the vessels of the myocardium, the skeletal muscles, and the liver (Lundholm, 1957), while in most other areas it acts as a constrictive agent, generally more potent than norepinephrine This *dilator action of epinephrine* in muscles is significant at blood concentrations which are barely sufficient to constrict the vessels of other areas. Even a maximal dilatation of the vessels of the muscles can be obtained sometimes by physiologic concentrations, and since normal secretion

though of course it is influenced by external factors. The fact that the arteriovenous anastomoses of the skin are almost maximally dilated when not exposed to sympathetic activity or blood-borne constrictor agents, suggests that *their muscle cells have little myogenic activity.* These vessels are connected with the mechanism of central temperature regulation and are controlled by the hypothalamic heat-loss center through constrictor fibers. Automaticity would only interfere with the central control of these specialized vessels. It is possible that a gradient *of decreasing automaticity* may *exist from the* capillary level, where it is pronounced, to the arterioles, where nervous influence predominates (Akers and Lee, 1935, Webb and Nicoll, 1952) Thus, there is reason to believe that the contractile elements of different vascular regions widely differ in their functional specialization *It follows that generalizations regarding* the vascular tone should *not* be made from observations of one vascular region or—even less—from the behavior of isolated large vessels

Rhythmically active, isolated large vessels give rise to *local potentials*. In other types of smooth muscles, it has been observed that, *when a certain potential threshold is reached*, propagated, all-or-none spikes are formed, and a mechanical response follows (Bozler, 1948; Bulbring, 1955), similar to that of other smooth muscles It has not been possible as yet to study the *bioelectrical phenomena* of the smooth muscles of the small blood vessels, but there are good reasons to believe that their spontaneous contractions are preceded by similar changes of membrane potentials

Purely muscular propagation of activity to adjacent smooth muscle cells of the vessels seems possible, at least to a limited extent (Fulton and Lutz, 1941–1942, Monnier, 1943, Burgi, 1944), even though little is known about the functional significance of such phenomena.

Influence of Distention on Vascular Tone. Bayliss (1902), followed by many others, suggested that the stretching effect of intravascular pressure may act as stimulus on the smooth muscle cells Reactive hyperemia after obstruction of the arterial inflow should be in part the result of the reduced pressure, even though local chemical changes are quantitatively far more important. The responsiveness of the vessels to more blunt mechanical stimuli is obvious to anyone who has tried to insert a cannula in a vessel. The stimulating influence of stretch on vascular tone varies from region to region and seems to exist only in areas where there is evidence of pronounced smooth muscle automaticity.

NERVOUS CONTROL

The nervous control of the small blood vessels has been repeatedly discussed (Barcroft and Swan, 1953; Uvnäs, 1954; Folkow, 1955, 1956). Most authors agree that the sympathetic fibers form distinct motor units, though marked *divergence and convergence of the ramifications seem to exist* (Hillarp, 1946). Sympathetic constrictor fibers are distributed in different degrees to all vascular regions, with the exception of the placenta. On the other hand, the vasodilator fibers are restricted to special areas and do not form a functionally uniform *group.*

Vasoconstrictor fibers excite the smooth muscle cells through the release of *norepinephrine,* possibly mixed with *epinephrine* in certain vascular regions (von Euler, 1950, 1956). Not only resistance but also capacity vessels are influenced (Landis and Hortenstine, 1950, *Alexander,* 1954–1955), so that the vasoconstrictor fibers can influence the venous return and, therefore, the cardiac output. The sphincter regions also seem to be influenced by the constrictor fibers (Folkow, 1956a). This control is of importance in the pulmonary vascular bed, where such a mechanism would mean a central control of the surface available for gas exchanges Vasoconstrictor fibers exert a powerful control over the arteriovenous anastomoses of the skin, but little is known about nervous influence on the shunt vessels of other tissues.

The distribution of constrictor fibers in different vascular beds seems to vary in inverse proportion to the importance of the tissue (Folkow, 1955) Thus, tissues like the brain and the myocardium are only poorly influenced by vasoconstrictor fibers, while a considerable, easily mobilized blood flow reserve is here created by a pronounced basal vascular tone. On the other hand, vessels with little importance *for the local tissue nutrition* but engaged in centrally controlled redistributions of flow (e g, the arteriovenous anastomoses of the skin) have an abundant supply of vasoconstrictor fibers

Under resting conditions, the small blood vessels (with some possible exceptions such as renal vessels, Smith, 1951) are continuously exposed to a constrictor fiber discharge of about one to two impulses per second, which is controlled predominantly by the medullary vasomotor center No vasodilator fibers participate in this tonic control of the small vessels (*Folkow, 1955*). The constrictor control of the cutaneous vessels, especially of the shunts, is primarily governed by the hypothalamic heat-loss center, and, therefore, the discharge of these fibers depends predominantly upon the level of heat exchange (Hensel, 1952).

In many regions of great importance for the total peripheral resistance, such as the splanchnic area, the kidneys, the skeletal muscles, and the skin, the effect of even *moderate changes* in the rate of discharge of nerve impulses is *considerable The medullary vasomotor center can therefore* cause remarkable changes in peripheral resistance with relatively small *changes of its activity*. The pulmonary resistance vessels are comparatively little affected by the constrictor fibers (Daly et al., 1952), and there seems in fact to be little need *for such a control* The constrictor control of the sphincter and capacity vessels of the lungs should then be far more important but is insufficiently known (Folkow, 1955, Duke, 1958).

Dilator Fibers. In some regions, where the basal vascular tone is so pronounced that the inhibition of constrictor tone *does not result in* maximal dilatation, *the small vessels* are controlled also by specific *vasodilator fibers Cholinergic dilator fibers of sympathetic* origin are *distributed* to the vessels *of the skeletal muscles* (Uvnas, 1954) The fact that these fibers may *induce* maximal dilatation *indicates that not* only the arteriolar section of the *resistance* vessels is affected but probably *also the sphincter* regions and the small *veins In other words, these* dilator fibers may *increase blood flow* and also spread this flow *over a bigger capillary* surface, also, concomitantly, *the* volume of blood in the *muscle* may increase somewhat The central connections of these *fibers suggests* that they may be *able* to secure an increased blood flow to the *muscles* in "emergencies" and possibly also *in normal* muscular work.

Parasympathetic cholinergic vasodilator fibers seem to be distributed to some specialized tissues, such as the salivary glands, the tongue, and certain parts of the genital organs (Folkow, 1956a). These fibers induce a decrease of the resistance to flow, and their main function may be that of adapting the regional blood flow to the degree of tissue activity.

A third type of dilator fibers, distributed primarily to the vessels of the skin and mucous [illegible] dorsal root dilator [illegible] ifi- [illegible] ell-known axon reflex of the pain fibers, and are thus independent of central control. These fibers, affecting primarily the smaller arterioles and sphincters, cause regional dilatation when noxious stimuli affect superficial tissues. This local dilator response is involved in the *triple response of Lewis and favors the processes of* defense and repair in the damaged tissue area. The transmitter substance is not identified but seems to be related to ATP.

Local Nerve Plexus. It has been suggested that the small vessels are also controlled by local autonomous nervous mechanisms Histologic studies do not *support such a theory, even* though certain indirect pharmacologic *observations suggest the existence* of interconnections between muscle cells (Folkow, 1955; *Furchgott, 1955*) The nature of these connections is uncertain at the present time

SPECIFIC VASOACTIVE AGENTS IN THE BLOOD STREAM

Several substances of interest for the control of the small vessels may be released into the blood stream The adrenal medulla contains *cells secreting both* epinephrine and norepinephrine in proportions which vary from *species to species* and which seem to be under a selective nervous control (Folkow, 1955). In man, the adrenal medulla seems to secrete principally epinephrine (Hokfelt, 1951; von *Euler, 1956*) Epinephrine differs from norepinephrine because it dilates the *vessels of* the myocardium, the skeletal muscles, and the liver (Lundholm, 1957), *while in most* other areas it acts as a constrictive agent, generally *more potent than norepinephrine This dilator action of epinephrine* in muscles is significant at blood *concentrations which are barely sufficient* to constrict the vessels of other areas Even *a maximal dilatation* of the vessels of the *muscles can* be obtained sometimes by physiologic *concentrations, and* since normal secretion

rarely results in high blood concentrations, dilatation may be considered quantitatively the most important vascular effect of the secretion from the adrenal glands (Celander, 1954; Lundholm, 1957). The sensitivity of small vessels to these hormones varies considerably in different areas For example, concentrations which exert powerful action on the cutaneous vessels have little influence on the renal vessels. All consecutive sections of a given vascular bed seem to be affected, including shunts, sphincters, and capacity vessels The action of these hormones on the resistance vessels is considerably weaker than that of the vasomotor nerves at any given discharge rate.

During the last decade, the possible significance of VEM ("vasoexcitor material") and VDM ("vasodepressor material") for the control of the small vessels has aroused much discussion (Shorr et al, 1951, Zweifach, 1951). However, the evidence of their vascular effects has been based almost entirely on the rat mesoappendix test, a method which has been seriously criticized (Baden, 1954, Zweifach and Metz, 1955, Crimson and Dryer, 1955), and the question of their functional significance needs careful reconsideration

Several other vasoconstrictor substances produced in the organism, like *vasopressin*, *serotonin*, and *angiotensin*, may be released into the blood in concentrations sufficient to create vascular effects. It is questionable, however, whether under normal physiologic conditions the secretion of vasopressin is ever sufficient to influence significantly small blood vessels Therefore, the vascular action of this substance may be chiefly of pharmacologic interest.

Serotonin seems to have a direct vasoconstrictor effect, though this may be masked by reflex changes of tone Normally its function seems to be dependent upon its local release from thrombocytes in case of vascular lesions, and is thus related to the initial phases of hemostasis.

It is unlikely that angiotensin is normally present in the blood in amounts sufficient to perform a physiologic role This is probably true also of most other vasoconstrictor agents as indicated by the fact that the acutely denervated vessels of the paw of the cat, which are very sensitive to constrictor agents are almost maximally dilated under "resting" conditions. However, it should be recognized that the study of these humoral agents presents numerous technical difficulties and that many questions still exist regarding their role in the regulation of the small vessels.

Local Dilator Mechanisms. There are few mechanisms more important for the maintenance of a normal *milieu intérieur* of the tissues than those responsible for the adaptation of the tonus of the small vessels to local changes in tissue metabolism. Though in some regions, such as the skeletal muscles, a central influence exerted by specific vasodilator fibers may facilitate the establishment of an increased blood flow during muscular activity, there is no doubt that control of this vascular adaptation is chiefly local. Even if all vasomotor fibers are out or degenerated, the small vessels dilate promptly upon activation of a tissue. More or less specific vasodilator agents may here be involved but are still insufficiently known No doubt, the tone of the small vessels is dependent on such basic factors of internal environment as P_{O_2}, P_{CO_2}, and pH (McDowall, 1956; Lundholm, 1957). The systemic vessels dilate when exposed directly to decreased P_{O_2}, to a lowered pH, or to increased P_{CO_2}. In all probability, all sections of a vascular bed are affected, so that not only the blood flow but also the volume of the blood and the perfused capillary surface in the affected tissue are increased Because of these reactions, a blood pressure increase in a tissue like the brain may induce an *increase* in regional resistance, quite independent of extrinsic nervous or humoral factors. The increased pressure gives a bigger cerebral blood flow, which increases the P_{O_2} of the tissue and reduces its P_{CO_2}. As the cerebral vessels are especially sensitive to such shifts, they constrict somewhat. The small vessels in less sensitive regions follow shifts in blood pressure more passively. *This means* that the pressure-flow relationship varies both with the region and with the actual level of tone and reactivity of a given vascular bed (Folkow and Lofving, 1956)

The above-mentioned *direct* effects on the small vessels, caused by local shifts in P_{O_2} and P_{CO_2}, and pH, should be distinguished from the *indirect* effects, mediated by the vasoconstrictor fibers and caused by general changes in the chemical composition of the blood and tissue fluids (McDowall, 1956) These indirect effects are opposed to the *locally induced* effects, and the resulting net change in vascular tone

in different regions is chiefly dependent upon the responsiveness of the smooth muscle cells and the extent of the vasoconstrictor fiber distribution to the small vessels Thus, for example, in tissues of immediate vital importance, such as the central nervous system and the myocardium, the vessels are poorly influenced by vasoconstrictor fibers and the local vascular effects will predominate during, for example, asphyxia, with a dilatation as a result. On the other hand, in regions like the skin and kidneys, asphyxia leads to decreased blood flow, because here the indirect effects, due to increased vasoconstrictor fiber discharge, are usually predominant The *pulmonary vessels* (or at least a hemodynamically important section of them) seem to react *in the opposite way to local changes of P_{O_2} and P_{CO_2}* as compared with the systemic vessels *A lowered P_{O_2} (or an increased P_{CO_2}) induces a vasoconstrictor response, which is mainly independent of vasomotor nerves* (Duke, 1956). *It follows that reduced ventilation causes reduced regional blood flow so that excessive shifts in perfusion-ventilation ratio are avoided*

Dilator Factors Released on Tissue Lesion. Damage to the tissues releases vasodilator factors, such as *histamine* or a closely related agent (Lewis, 1927), and *probably* also certain polypeptides with similar actions (Wilhelm, Miles, and Mackay, 1955) These agents dilate the small vessels by a direct influence on the smooth muscle cells ("red reaction" in the triple response). These substances can also dilate the vessels by way of the previously discussed axon reflexes, a mechanism which becomes significant only in tissues rich in pain fibers, such as the skin and superficial mucous membranes The endothelium is also affected by these substances, resulting in protein leakage and edema (Lewis, 1927).

The Influence of Temperature Changes on the Small Vessels. The influence of changes of temperature on the small vessels is relatively complex. Increased temperature probably increases smooth muscle automaticity, but this direct effect is counteracted by the simultaneously increased metabolism of surrounding tissues, and this increases the production of vasodilator agents As a net result, an increased blood flow is generally obtained *on raised temperature* Lastly, at *extreme temperatures,* whether high or low, *tissue damage is superimposed* on the mechanisms described above Induced "red reaction" and axon reflex dilatation are probably responsible for the "hunting reaction" seen when the skin is exposed to cold As the resulting increase of blood flow again warms up the tissue, the release of vasodilator agents and the dilator response subside. Then the temperature again decreases to levels where tissue damage is inflicted, and the cycle is repeated

CONCLUSIONS

In spite of a great number of studies dealing with the control of the small blood vessels, it is obvious that many basic functional characteristics are still incompletely known. Hitherto most studies have dealt with the regulation of the resistance vessels, and knowledge about the equally important sphincter regions, capacity vessels, and different types of shunts is indeed fragmentary

CONTRACTILITY OF THE CAPILLARIES

The mechanism of capillary contractility is an issue of controversy that started when Rouget (1873) made a careful study of blood capillaries in the hyaloid membrane of the eye in adult amphibians. He described cells which formed a second layer outside the endothelium, oriented spirally to the long axis of the vessel, and frequently encircled the capillaries Rouget believed these cells to be contractile. Subsequent investigators believed these cells to be branched smooth muscle cells or merely adventitial cells

Vimtrup (1922) reported that contraction starts at one of the branched nonpigmented *adventitial* (Rouget) cells and, as a chain reaction, *spreads* down the capillary Bensley and Vimtrup (1928) observed actual contraction in the cells of Rouget of capillaries of the tongue of the living frog and, by mechanical stimulation, in the capillaries of the surviving nictitating membrane By means of supravital staining with janus green B, they demonstrated a similarity of staining in the muscle cells of the smaller arteries and in the Rouget cells of the capillaries Krogh (1929) stated that the branching Rouget cells form a definite

rarely results in high blood concentrations, dilatation may be considered quantitatively the most important vascular effect of the secretion from the adrenal glands (Celander, 1954; Lundholm, 1957). The *sensitivity of small vessels* to these hormones varies considerably in different areas. For example, concentrations which exert powerful action on the cutaneous vessels have little influence on the renal vessels. All consecutive sections of a given vascular bed seem to be affected, including shunts, sphincters, and capacity vessels. The action of these hormones on the resistance vessels is considerably weaker than that of the vasomotor nerves at any given discharge rate

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injury frequently result in ... which can readily be induced by chemical or mechanical trauma using micromanipulative procedures.

A striking characteristic of the circulation in tissues maintained under normal conditions is the intermittency of capillary blood flow. The circulation becomes confined periodically to a small segment of the bed, during which time the majority of the capillary vessels show no active movement of blood through them The periodic nature of the capillary circulation is the consequence of changes in the caliber of the terminal arterioles, the metarterioles, and the precapillary sphincters The remainder of the vessels in the capillary bed do not exhibit active changes in caliber coincident with the vasomotor cycles Many investigators have described a temporary plugging of narrow precapillary offshoots by the leucocytes (Illig). This type of disturbance in capillary flow is highly unpredictable and can in no way account for the periodic ebb and tide of over-all capillary blood flow and bypassing of the true capillaries It is apparent that aside from passive physical resistance and possible swelling of the endothelium (Sanders et al), the capillaries do not play an active role in distributing blood through the microcirculation The endothelial vessels do not respond to electrical or chemical stimuli by rapid changes in caliber, and there is no well-substantiated evidence that modified muscle elements of the Rouget-cell type are distributed throughout the capillary network Many of the smooth muscle elements in the metarterioles are branched and have an atypical appearance It is possible that these were the cells which Krogh, Vimtrup, and Fleisch (1927) believed to be generally distributed effector units for regulating the caliber of the capillaries

It is interesting that in the embryonic development of the circulatory tree, the transformation of the terminal network of capillaries into more highly differentiated vessels occurs in those channels through which a rapid circulation of blood exists Perivascular mesenchymal elements in the walls of these vessels become transformed through a series of stages into typical smooth muscle cells (Zweifach, 1937) The vessels begin to show contractile reactions before the muscle cells have become completely differentiated The possibility exists that the branched pericytes visible in the adult capillary bed are partially differentiated smooth muscle cells of this type which still possess the potentiality of being transformed into typical smooth muscle elements, but which are not completely effective contractile units.

INNERVATION

The distribution of nerve fibers to the various constituents of the terminal vascular bed has not been satisfactorily worked out Sympathetic nerve fibers, terminal endings on smooth muscle, and perivascular plexuses can be demonstrated in all categories of arterial vessels down to the size of terminal arterioles

Anatomic studies with silver impregnation methods (Woolard), or supravital staining with methylene blue (Wiedeman), fail to indicate a consistent relationship between terminations of the sympathetic fibers and the smooth muscle elements in the metarterioles and precapillaries (Benninghoff) Many of the precapillary and metarteriolar smooth muscle cells show no contiguous nerve fibers. The difficulty in staining the fine ramifications of the sympathetic nervous system leaves open the possibility that the apparent erratic distribution of nerves in this area may be due to technical con- ... be- ... n of the sympat ... icate a nonuniform response of the metarterioles and precapillaries Fulton and Lutz have cited experiments with microelectrodes in which stimulation of the peripheral nerve plexus in the hamster cheek pouch elicited vasoconstriction and vasodila- ... but not in con-

... ear following stimulation of the cervical sympathetic nerve, again most frequently at points of bifurcation on the arterial side.

A number of reports, based on histologic evidence, indicate an afferent innervation of the microcirculation through delicate nerve networks intermingled with the capillary vessels. The literature contains frequent references (Fleisch, 1927) to locally mediated reflex vasodilatation of the arterioles feeding blood into the capillary bed, presumably by means of a nervous mechanism The precise path by which such reflexes influence the terminal arterioles remains controversial

smooth muscle layer which is frequently arranged as a wide-meshed network leaving a large part of the endothelium uncovered Fulton and Lutz (1942), by stimulating minute nerves of the frog, produced limited vascular responses which suggested to them the concept of smooth muscle motor units in small blood vessels.

A second group of investigators think that the endothelial cells are independently contractile (Florey and Carleton, 1926), and state that there is no positive evidence of the participation of Rouget cells.

Two types of independent capillary contractions have been described (Clark and Clark). The first would be an *active contraction* characterized by a wavy contour of the vessel wall which may occur spontaneously or be produced experimentally. The second would be a *passive contraction*, in which the vessel outline remains smooth at all stages of narrowing The latter is characterized by a simple decrease in vessel caliber. According to Clark and Clark, both types may occur without regard to presence or absence of any adventitial cell on the vessel wall or to the particular location of such cells In fact, the above investigators state that "contractions were observed in vessels before any Rouget cells develop while, after formation of Rouget cells, contractions are frequently initiated at a distance from them " They conclude that *the capillary endothelium has a definite power of contractility which is independent of any form of adventitial cell and that caliber changes are due to alterations in blood flow and pressure caused by active contraction of supplying arteries* [1]

A third group of investigators ascribed the contractility of capillaries to the precapillary sphincters Here the amount of blood entering the capillary branches is controlled by the state of contraction of smooth muscle cells of the precapillary sphincters (Zweifach). In muscle, capillaries are kept empty by the lateral expansion of the shortening and thickening muscle fibers. The blood is forced out of the capillaries, but as the muscle fibers relax, the compression of the vessels is released and blood spurts from the dilated arterioles in the flaccid, dilated capillaries.

In the specialized capillaries of the liver (sinusoids), active occlusion has been observed by Knisely et al. (1948). Liver sinusoids are also specialized in other respects: the cells lining them (Kupffer cells) are all potential phagocytes. They were thought to constitute a symplasm, since no boundaries had been demonstrated between them with the light microscope. However, Rüttner and Vogel found by electron microscopy that the Kupffer cells are discrete cells which overlap marginally, much as roof shingles do. These authors have described an astonishing mechanism for the stoppage of blood flow in the liver sinusoids: a *single Kupffer cell may contract in such a way that its cell body bulges into the lumen of the sinusoid and thus may occlude it.* This mechanism may replace Knisely's concept of "outlet sphincter." Knisely's technique of transillluminating living organs shows blood flow and stagnation. It can give no information on the cytologic mechanism responsible for stagnation.

Another kind of endothelium (perhaps syncytial) is the "endenchyma" of the renal glomerulus (Elias, 1957) The endenchyma is a mass of cells through which blood flows in often-changing and shifting tunnels. In transilluminated frog kidneys (unpublished observations by the author), one can observe that when blood flows slowly through the glomerulus, the channels are wide and constant in their position. During rapid flow, the blood channels are narrower and more numerous, and their positions shift rapidly.

VASOMOTION OF THE CAPILLARIES

The capillaries exhibit no rapid changes in caliber following either local or systemic stimuli. During periods of relative ischemia, the empty vessels may narrow gradually until the lumen is almost obliterated With the relaxation of the precapillary sphincters and the reentry of blood, the inactive capillaries immediately open to their maximum normal diameter. *Despite major fluctuations in blood flow, the true capillaries maintain a constant diameter.* Under abnormal conditions, when the endothelium or its associated elements are

[1] A different viewpoint will be presented below by Dr. Zweifach The controversial status and the importance of this problem required presentation of both points of view. *Editor.*

Starling argued that the blood-tissue barrier could be penetrated freely by water and most of the solutes of plasma, but that the colloidal components, chiefly the plasma proteins, were selectively retained by this barrier He showed that such a system would give rise to an *osmotic pressure* tending to move fluid from the tissue spaces into the blood Opposing this osmotic force, the *hydrostatic pressure* within the capillary tends to filter fluid from the blood. A balance between these two factors is achieved, so that ordinarily in resting tissue there is no net movement of fluid The *rate* at which fluid moves across this barrier is quantitatively determined by (1) the difference between these two opposing forces, i e , the effective driving force; (2) the area of capillary wall available for filtration, and (3) the filtration characteristics of the barrier

Each of these factors has been studied independently, and the findings, in general, confirm the basic physical nature of the system The evaluation of these factors has required complex experimental approaches, because estimation of the driving force requires measurement of the effective osmotic and hydrostatic pressures within the capillaries, and each of these in turn is an algebraic summation of several physiologic variables

The Driving Force. OSMOTIC PRESSURE The colloid osmotic pressure (or *oncotic pressure*) is determined by the concentration of those particles in the plasma which cannot penetrate the *capillary wall* Where trauma increases permeability of the capillaries, permitting the escape of proteins, the *effective colloid osmotic pressure* is markedly *decreased* (Courtice).

By virtue of *its greater* absolute and molar concentration, the plasma *albumin* plays the most important role in determining the oncotic pres...

... the effective pressure *approaches* the value obtained when the same colloid *acts at* a completely impermeable membrane *in vitro* (Pappenheimer, 1953) The *normal* human plasma proteins give rise to an *oncotic pressure* of approximately 30 to 40 cm water, and except when trauma of the capillary wall allows abnormally *large* amounts of the colloids to escape, the pressure manifested in vivo is about 90 per cent of the predicted value. The presence *of* small amounts of protein in the tissue fluid tends to diminish the effective osmotic pressure, but in most normal tissues this factor can be estimated only by indirect methods. To date it has not been technically possible to obtain a sample of normal tissue fluid. In any tissue, for example, the liver, where large amounts of protein escape across the capillary wall, so that the concentration of colloid in the tissue fluid is high, the effective osmotic pressure must be considerably less than the maximum in vitro estimates (Morris).

CAPILLARY HYDROSTATIC PRESSURE The effective transmural hydrostatic pressure is the difference between that within the capillaries and the counterpressure in the tissues. The capillary pressure must be greater than the venous and less than arteriolar pressure, but the exact value is determined by the ratio of the postarteriolar and prevenular resistances It is therefore impossible to predict even the qualitative change in capillary pressure from measurements of changes in arterial pressure alone Simultaneous change of arteriolar caliber could profoundly influence the capillary pressure. It is, however, safe to argue that *any increase in venous pressure must be accompanied by an increase in the intraluminal pressure in the capillary* In general, direct and "indirect" measurements of the capillary hydrostatic pressure give values ranging from 16 to 44 *cm* water (Landis, 1934). The possibility *of local regulation* has been proposed, whereby contraction of the precapillary sphincter *may* reduce the flow and the pressure within the single capillary even to zero (Chambers). This may account for much of the variability found in the measured values.

The tissue fluid pressure, or tissue "tension," acts to diminish the effective transmural pressure and so modifies the rate of filtration across *the vascular* wall The tension in the several tissues differs greatly. In the *subcutaneous* parts, it is about 3 cm water, within the sheath of a skeletal muscle, it is above 50 cm water Furthermore, there are great variations within *a single tissue*, as in the case of muscle, *where* tissue tension may exceed the systolic blood pressure during maximal contraction, or in the case of the skin of a dependent extremity, where the *increase is sufficient* to balance the increased *venous (and* presumably capillary) pressure The increase in the volume of *tissue fluid* resulting from the outward filtration of fluid *is apparently* self-limited, because the

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Exchange of materials across the capillary wall

CHESTER HYMAN

A consideration of the exchange of materials across the capillary wall is basic in almost every area of physiology. It is obvious that everything needed by, or produced in, the tissues must be transported by the circulation and must cross the blood–tissue-fluid barrier. The entire cardiovascular system is so regulated as to provide the most satisfactory conditions for such an exchange, while the morphologic arrangement of the capillary beds shows special adaptations to facilitate this function It has been estimated that no part of an active muscle is located more than 12 μ from a capillary, so that the diffusion distances are of cellular dimensions. The small caliber of the fine vessels provides maximum surface area per unit volume of blood, and the large total cross-sectional area at this stage of the circulation assures a relatively slow velocity of blood flow in the capillary bed The barrier separating the blood from the tissues is made up of a single layer of extremely thin endothelial cells cemented to one another with a constantly renewed porous material This barrier provides only minimal hindrance to the movement of fluids and the diffusion of most solutes. Yet, the capillary wall plays an important role in the regulation and maintenance of the circulating blood volume Its characteristics are apparently a compromise between the ideal for free solute exchange and the barrier required to contain and hold a circulating fluid

REGULATION OF BLOOD VOLUME

The circulating blood volume is maintained with remarkable constancy despite large and rapid fluctuations in the total fluid content of the body. Normally, the intake of water and electrolytes is precisely balanced by excretion to maintain the body water and salt content with extremely small variations. These relations between the organism and its environment are at least partially dependent upon changes in the blood volume· an increase in this fluid compartment will ultimately lead to a diuresis or a modification of salt or water intake. However, temporary alterations of the blood volume may occur, and these are rapidly compensated by simple physicochemical shifts of fluid between the several body water compartments (Brown).

Individual water molecules move with minimal restriction back and forth across the capillary wall separating the blood from the tissue fluid and across the membranes between the extracellular and the intracellular compartments. The actual volume of fluid contained in each of the compartments at any time, however, is normally quite constant and is the resultant of the interplay of the amount and nature of the solutes found in the compartment and the permeability characteristics of the bounding membrane Thus, *the plasma volume reflects the relationship between the circulating plasma protein mass, the protein retention by the capillary wall, and the effective hydrostatic pressure within the minute blood vessels* (Scatchard et al) The essential features of the automatic regulation of plasma volume were established by Starling (1896) and have been repeatedly confirmed in the intervening years (Landis et al , 1932, Hyman, Pappenheimer, 1953).

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By virtue of its greater absolute and molar concentration, the plasma *albumin* plays the most important role in determining the oncotic pressure in the vascular system (Weech). Although some small fraction of the protein does escape across the normal capillary wall (Berson), the effective pressure approaches the value obtained when the same colloid acts at a completely impermeable membrane in vitro (Pappenheimer, 1953). The normal human plasma proteins give rise to an oncotic pressure of approximately 30 to 40 cm water, and except when trauma of the capillary wall allows abnormally large amounts of the colloids to escape, the pressure manifested in vivo is about 90 per cent of the predicted value. The presence of small amounts of protein in the tissue fluid tends to diminish the effective osmotic pressure, but in most normal tissues this factor can be estimated only by indirect methods. To date it has not been technically possible to obtain a sample of normal tissue fluid. In any tissue, for example, the liver, where large amounts of protein escape across the capillary wall, so that the concentration of colloid in the tissue fluid is high, the effective osmotic pressure must be considerably less than the maximum in vitro estimates (Morris).

CAPILLARY HYDROSTATIC PRESSURE. The effective transmural hydrostatic pressure is the difference between that within the capillaries and the counterpressure in the tissues. The capillary pressure must be greater than the venous and less than arteriolar pressure, but the exact value is determined by the ratio of the postarteriolar and prevenular resistances. It is therefore impossible to predict even the qualitative change in capillary pressure from measurements of changes in arterial pressure alone. Simultaneous change of arteriolar caliber could profoundly influence the capillary pressure. It is, however, safe to argue that *any increase in venous pressure must be accompanied by an increase in the intraluminal pressure in the capillary.* In general, direct and "indirect" measurements of the capillary hydrostatic pressure give values ranging from 16 to 44 cm water (Landis, 1934). The possibility of local regulation has been proposed, whereby contraction of the precapillary sphincter may reduce the flow and the pressure within the single capillary even to zero (Chambers). This may account for much of the variability found in the measured values.

The tissue fluid pressure, or tissue "tension," acts to diminish the effective transmural pressure and so modifies the rate of filtration across the vascular wall. The tension in the several tissues differs greatly. In the subcutaneous parts, it is about 3 cm water, within the sheath of a skeletal muscle, it is above 50 cm water. Furthermore, there are great variations within a single tissue, as in the case of muscle, where tissue tension may exceed the systolic blood pressure during maximal contraction, or in the case of the skin of a dependent extremity, where the increase is sufficient to balance the increased venous (and presumably capillary) pressure. The increase in the volume of tissue fluid resulting from the outward filtration of fluid is apparently self-limited, because the

tissue tension quickly rises to significant levels. If the distention of the tissue persists, the tension falls as the elasticity of the connective tissue fibers is altered, and edema may progress. These relationships have been well presented by McMaster.

Area and Permeability of the Blood-Tissue Barrier. Any change in the driving force would change *both* the rate of filtration of fluid across the capillary wall and the steady-state transcapillary distribution of fluid. Thus, decreased effective colloidal osmotic pressure, for example, would cause a more rapid formation of tissue fluid and, ultimately, would diminish the circulating blood volume.

The rapidity with which fluid distributes itself across the capillary wall in response to minimal changes in driving force is due in part to the great area available for filtration and in part to the specific characteristics of the membrane (Pappenheimer, 1956) It has been estimated that in each 100 Gm of active peripheral tissue, there are at least 6,000 cm^2 of membrane, but this area probably varies from moment to moment because of the continuous alterations in the pattern of blood flow through the terminal vascular bed Such *changes in filtration area will affect the rapidity* with which fluids shift between compartments but cannot alter the final steady-state distribution

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The free exchange of solutes across the blood-tissue barrier is accomplished by a mechanism of simple diffusion and, in its quantitative aspects, depends on the extent to which the barrier restricts diffusion of the

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19

Gradients of pressure in the cardiovascular system

JOSÉ L. DUOMARCO AND RICCARDO RIMINI

The *hydraulic gradient* (H G) of the cardiovascular system is usually represented with the purpose of giving a schematic view of its variations as a result of the various resistances existing in different vascular segments. This schematic presentation of the H G includes various details based on research of *systemic*, pulmonary, and portal pressures, and of the phenomenon of collapse which affects the entire venous return The study of gradients is based on the plotting of the heights of the *meniscus* of a series of piezometers in lateral communication with parts of the cardiovascular system (ordinates) *against the* different segments of that system, presented in the same order as that *encountered* by the blood flow (abscissis) (Fig 2-65) The diagram is easily understood when the subject is in the *supine* decubitus (Figs 2-66A, 2-68A) but *requires* special attention if the subject is in *the standing* position In *the* latter case, the different segments of the circulatory system must be transferred to the axis of the *abscissa* by means of a 90° rotation, this would be equivalent to an ordered horizontal arrangement of the manometers at intervals *equal* to the *corresponding* differences in level between the vascular points where *pressures* were gaged (Figs 2-66B, 2-68B and C) The level *of the* heart is taken as the *reference level*, following a tradition started by Hales With this convention, the subatmospheric pressures of the pleural cavity and of the cardiac cavities (when in diastole) are represented by negative values Thus, *the* heart, nominally placed at the "O" level, is potentially lowered to the value of the low pleural pressure.

The H G. of the circulatory *system* as a whole is represented in Fig 2-65 Each *ventricle* has two gradients, which alternatively

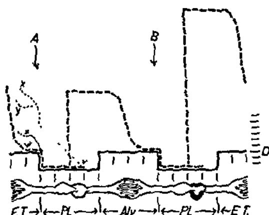


Fig 2-65. Hydraulic *gradient (H G)* of the *circulatory system* The vascular and cardiac segments are *represented* along the axis of the *abscissas. E,T*, Extrathoracic medium, *Pl., pleural* medium, *Alv.*, *alveolar* or intrapulmonary medium; *A*, juxtapleural collapse of the systemic veins, *B*, juxtapleural collapse of the pulmonary veins, *O*, cardiac level (*it has been supposed that the abdominal "zero" level and* the systemic and pulmonary venous level, *in* the supine decubitus, coincide *with the cardiac level*). *Systemic* venous gradients transferred from Fig. 2-68, *w-v*, *I V C* (erect and decubitus) and S.V.C. (decubitus), *z-v*, *V P* (erect and decubitus), *y-v*, *B.V.* (descending arm), *x-v*, *S V C. (erect)*

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19

Gradients of pressure in the cardiovascular system

JOSÉ L. DUOMARCO AND RICCARDO RIMINI

The *hydraulic gradient* (H.G.) of the cardiovascular system is usually represented with the purpose of giving a schematic view of its variations as a result of the various resistances existing in different vascular segments. This *schematic presentation of the H.G. includes* various details based on research of systemic, pulmonary, and portal pressures, and of the phenomenon of collapse which affects the entire venous return. The study of gradients is based on the plotting of the heights of the *meniscus* of a series of piezometers in *lateral communication with* parts of the cardiovascular system (ordinates) against the different segments of that system, presented in the same order as that encountered by the blood flow (abscissas) (Fig. 2-65). The diagram is easily understood when the subject is in the supine *decubitus* (Figs. 2-66A, 2-68A) but requires special attention *if the subject is in the standing* position. In the latter case, the different segments of the circulatory system must be transferred to the axis of the abscissa by means of a 90° rotation, thus would be equivalent to an *ordered horizontal* arrangement of the manometers at intervals equal to the corresponding differences in level between the vascular points where pressures were gaged (Figs. 2-66B, 2-68B and C). The level of the heart is taken as the *reference level*, following a tradition started by Hales. With this convention, the subatmospheric pressures of the pleural cavity and of the cardiac cavities (*when in diastole*) are represented by negative values. Thus, the heart, nominally placed at the "O" level, is potentially lowered to the value of the low pleural pressure.

The H.G. of the circulatory system as a whole is represented *in Fig. 2-65. Each ventricle has two gradients,* which alternatively

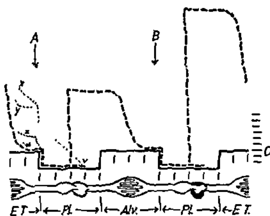


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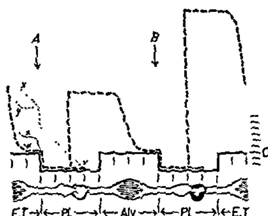


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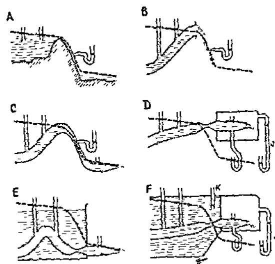


Fig 2-67. A to F Theoretical models where the *hydraulic gradient is interrupted by a discontinuity.* The last four cases reproduce the conditions that determine the venous collapses.

In each of the systemic and pulmonary *venous segments,* the H.G. is interrupted by an abrupt fall, so that the circulatory system cannot be considered as a continuous tubing In fact, two discontinuities constituting two striking drops occur in its course. These drops are caused by the collapse which affects all the large venous collectors This collapse is due to a series of physical conditions common to those vessels, viz.· (1) the venous walls are thin and easily depressible; (2) the effective venous pressure is small, because of moderate velocity of the flow and low pressure of the atrial chambers during almost all the cardiac cycle, (3) all veins pass from a medium of higher pressure (extrapleural) to one of lower pressure (intrapleural), (4) some *veins are descending tubes* surrounded by a gaseous medium (this is the case of the veins in the elevated limbs, and of the jugular vein and the superior cava in a *standing subject*) Figure 2-67 *shows* the hemodynamic characteristics of the phenomenon of collapse and the particular conditions of each of the great venous branches

Figure 2-67A indicates the characteristics of the H.G. of a river interrupted by a waterfall Under these circumstances, the H.G. follows the surface of the river and presents the following characteristics an upstream dam segment, the inclination of which depends upon the velocity of the flow, a *downstream dam segment* with similar characteristics, and a discontinuity corresponding to the waterfall, where *the* velocity of the liquid is great, the section is small, the lateral *pressure is* zero, and the difference of potential energy between both levels is lost by friction Figure 2-67B shows the H.G. of an ascending collapsible tube from which flows a free jet of liquid The situation is similar to that of the preceding figure, except that the H.G. of the tube must be determined by a series of piezometers *Figure* 2-67C *shows* the case of a collapsible tube with an abrupt fall in its course During the fall, the velocity of the liquid increases, the cross-sectional area is proportionally reduced the tube collapses, and the lateral pressure is zero, consequently the H.G. *follows* the *axis of the tube* The veins of the elevated limbs, also the jugular veins and the *superior cava* in the *standing* position, are good examples of collapsible tubes descending *in a* gaseous medium. What happens when such a tube (horizontal or ascending) passes from a gaseous medium of higher pressure (atmosphere) to one of lower pressure (pleural cavity) is shown in Fig 2-67D The collapse and the concomitant abrupt fall of the H.G. are produced immediately before this passage. The situation is similar to that of a waterfall between the real and virtual levels of the tube, the virtual level is determined by the pleural "negative" pressure (*manometer J*). *A similar condition is found in the superior cava* of a subject in the horizontal position Figure 2-67E shows the conditions of the liquid flow in a collapsible tube passing from a hydrostatic medium of its own density to an atmospheric medium It can be observed that the proximal portion of the H.G dies out in the free level of the liquid, and that the collapse of the tube and the discontinuity of the H G. are *produced* immediately before this passage. Besides, the precollapse portion of the tube contained in the hydrostatic medium is distended, independently of its ascending or descending course Figure 2-67F *shows the changes* introduced in the preceding case by the fact that the liquid and gaseous mediums are separated from the atmosphere. In the diagram, the free level of the hydrostatic medium is virtual (manometer *K*), and the level of the tube surrounded by the gaseous *medium is* potentially lowered by the low pressure of that medium (manometer *J*) This situation is similar to that in the *inferior cava,* passing *from* the abdominal hydrostatic medium to the pleural gaseous medium of lower pressure. In the theoretic models represented in Fig 2-67, the liquid flows *fundamentally* along the horizontal axis, and the H G has been traced in the horizontal *projection of the liquid* stream With the venous branches, the position of the subject should also be *considered*

The *H G of the inferior vena cava system in the* supine decubitus (Fig 2-68A) fulfills

correspond to diastole and systole; respectively, they are at the end and beginning of each of the two waves which characterize the H.G. in its entirety. The H.G corresponding to the *systemic arteries* is an almost horizontal line because of the practically hydrostatic character of the arterial content. This is determined by small local resistances and moderate velocity of the blood flow. The shape of this segment of the H.G. does not vary with the position of the body. In relation to this fact, Fig. 2-66 shows that, in the supine decubitus, the pressures are practically the same in all points of the arterial system, while in the standing position, they vary with the level of the points where blood pressure is measured. By virtue of well-known physiologic facts, the height of the arterial H.G. depends upon that of the carotid sinus; for this reason, the arterial H.G. becomes elevated with respect to the cardiac level when the subject passes from the horizontal to the standing position. The H.G. of the *pulmonary artery and its branches* is similar to, though naturally lower than, that of the systemic arteries. The great resistance of the systemic and pulmonary *arteriolocapillary-venular segments* determines a considerable fall of the corresponding gradients.

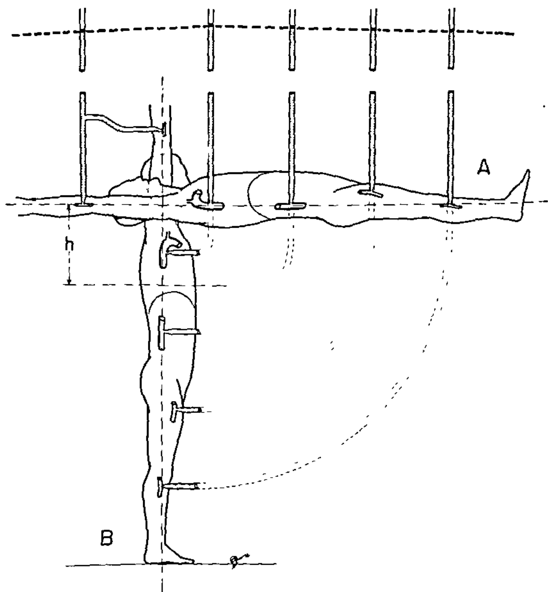


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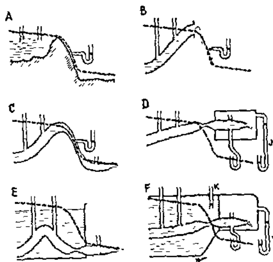


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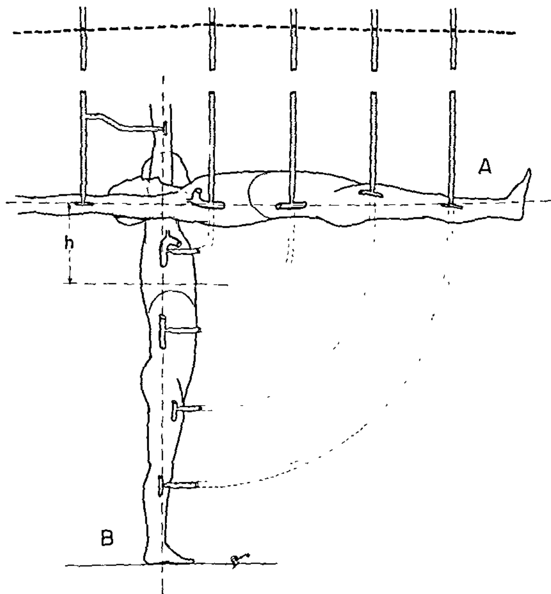


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inferior abdominal vena cava, approaching and joining it during the course of the liver vascularization, immediately before the diaphragmatic collapse

The H.G. of the *superior vena cava system* in the supine decubitus (Fig. 2-68A) fulfills the conditions of Fig. 2-67D. It presents an extrapleural segment that is slightly inclined and quite close to the venous plane; a discontinuity corresponding to the pleural venous collapse, and an intrapleural segment that is relatively long and close to the virtual level of the superior vena cava. If the subject moves to the standing position (Fig. 2-68B), the jugular veins, the superior vena cava, and the veins of the elevated arm collapse, the situation is similar to that in the descending portion of the tube in Fig 2-67C The effective vascular pressure is zero all along the venous course, and, therefore, the piezometric levels coincide with the points where pressures are measured Consequently, when levels are plotted against points of measurement, a straight line is formed with an angle of 45°. This line is interrupted by the *discontinuity due to the* potential fall of the collapsed vessels when passing from the extrapleural medium (atmospheric pressure) to the intrapleural medium ("negative" or subatmospheric pressure).

The conditions of the H G of the *distended veins in the lowered arm* (Fig 2-68C), after transferring the venous sections to a horizontal axis, are similar to those of Fig. 2-67D The tracing shows a slightly inclined extrapleural segment ending at the point of the juxtathoracic venous collapse

The differ…

Fig

syst.

The *H G of the pulmonary veins evolves* similarly to that of the systemic veins It is formed (Fig 2-65) by a higher segment, corresponding to the intrapulmonary portion of the veins, which is submitted to the atmospheric values of the intrapulmonary medium, a lower segment, corresponding to the intrapleural portion of the veins, which is submitted to the subatmospheric pressure of the pleural cavity, and the discontinuity between both segments, due to the collapse of the veins when passing from one medium to another

The H.G. of the systemic and pulmonary veins is followed by the *H G of the cardiac cavities*, which ends in the atria during the ventricular systole, or in the ventricles during the rest of the cardiac cycle.

Every point of the H.G. varies in time owing to cardiac and respiratory activity, describing a vascular or intracavitary pressure curve. This has been represented in a pressure-length-time system in Fig. 2-69. Sections *A* and *B* mark the penetration of the veins into the pleural cavity. It is evident that immediately before the entrance, venous pressures are similar to those of the corresponding extrapleural medium. Immediately after the penetration, the same holds true for venous pressure and pleural pressure Then, atrial activity is inscribed in the intrapleural venous pressure curve.

The H G of the circulatory system, integrated with the two waterfalls that interrupt its course, should be followed by a new analysis of some basic problems of normal and pathologic physiology

Figures 2-65 and 2-69 show how any variation in the circulatory flow and in the resistance of the different cardiovascular segments is followed by corresponding variations in the height and inclination of the H G. sectors, only points A and B and the v-v portion of the H G (where hydraulic pressure is zero) are independent of the circulatory variations and are determined only by the extravascular conditions This is what happens in a waterfall whose profile is independent of the flow of the river *Those "fixed points" of the cardiovascular system are necessary levels of reference for the measurement of peripheral venous pressure.* Figure 2-68 shows the small difference (never higher than 2 cm for animals and man in rest) between the heights of the venous meniscus and of those "fixed points" (abdominal "zero" level for the inferior vena cava system; subclavian-axillary level for the distended veins of the descended arm, and puncture level for the collapsed veins of the elevated arm)

Another consequence of the set of dams in the circulatory system is the following the extrapleural venous gradients (upstream dam) cannot be directly affected by respiratory variations of the intrapleural venous gradient (downstream dam) This is why *pleural low pressure, even if increased during inspiration or during Muller's test, cannot increase venous return and accelerate the systolic flow* On the other hand, the elevation of dams A and B

the same conditions as those of Fig. 2-67F. It presents a slightly inclined extrapleural segment that ends at the abdominal "O" level (virtual free level of the abdominal hydrostatic medium); a discontinuity corresponding to the juxtadiaphragmatic collapse of the inferior vena cava; and an intrapleural segment, which is very short in man. In the standing position (Fig. 2-68B), after the corresponding transfer of the vascular points to the axis of the abscissas, the H.G of the system of the inferior vena cava is identical to that of the subject in the supine decubitus. Consequently, pressures that are all similar and low in the supine decubitus must vary in standing position with the height of the point where they were measured. It is also observed that in both positions, the abdominal portion of the inferior vena cava is distended by the small difference between the intravascular pressure and the hydrostatic pressure of the abdominal medium (Fig 2-67F). The *H.G. of the portal vein*, for any position of the body (Fig. 2-68A and B), runs parallel to, and slightly above, the H.G. of the

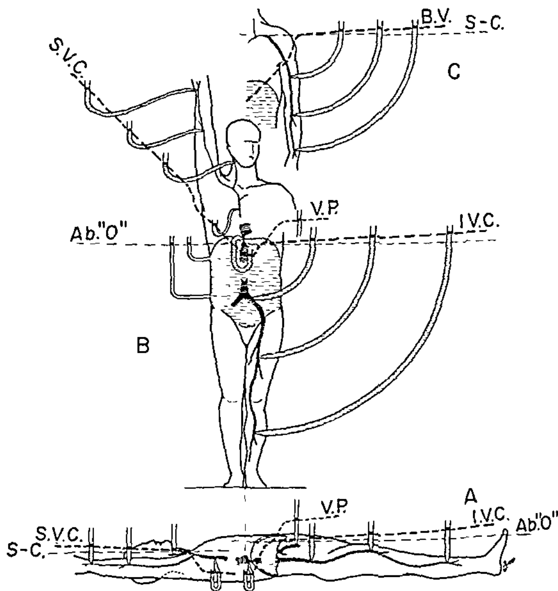


Fig. 2-68. A Hydraulic gradient (H.G.) of the systems of the superior cava, *S.V C.*, of the inferior cava, *I.V.C.*, and of the vena porta, *V.P*, in the supine decubitus. *B.* The same gradients in the standing position with elevated arm. C. The H G. of the brachial veins, *B.V.*, and of the S.V.C., in the standing position. Notice that the venous gradients are practically determined by extravascular levels abdominal "zero" level, Ab "O"; subclavian-axillary level, S-C. measurement points level, virtual level of the intrapleural veins, determined by the pleural negative pressure.

when the downstream dam is high enough, the collapses disappear and the pressure in the extrapleural venous segments is increased This happens (1) when there is a sufficient increase of cardiac output, (2) in ventricular failure as well as in mitral or tricuspid stenosis, (3) when lung retractility is reduced (emphysema, pneumothorax) and the extra- and intrapleural levels are nearer Different pathologic conditions and positions determine the order in which collapses disappear and local extrapleural pressures are increased. It is understood that from the point of view of peripheral venous pressure, a progressive right ventricular failure causes the following sequence (1) normal peripheral venous pressure; (2) increase of venous pressure in the abdomen and legs in the usual positions of the body, and of that of the arm in supine decubitus; (3) increase of the venous pressure in the arm even in the erect position, (4) progressive jugular distention, which finally increases spinal fluid pressure.

When the collapses disappear, the circulatory system becomes a continuous system of tubing It is then possible for inspiration to facilitate the venous return and for expiration to enhance cardiac systole, it is even possible that blood can be brought to circulate by the action of respiratory activity alone, as occurs in the classical model of Landois.

According to Harvey's concept of circulation, cardiac action was the only propulsory force acting on blood Demonstration of "negative" pleural pressure, by Carson and Donders, was followed by the concept, never experimentally demonstrated, that venous return is favored by respiratory activity. *Actually, in normal conditions, "negative" pleural pressure causes venous collapses which impede any favorable action of respiration on venous return.* An increase of the respiratory function tends to exaggerate the venous collapses, and may even reestablish them if they have disappeared as a result of heart failure

(increase of abdominal and intrapulmonary pressures) induces a retrograde engorgement.

The system of dams acts upon the waves moving along the cardiovascular bed. A pressure variation in any sector of the cardiovascular system creates a pressure-volume wave, which is transmitted in both directions, with such a velocity that it travels along the whole system in not more than 2 sec. But, while the *forward section of the wave meets with no* obstacle except for the damping effect of the capillary bed, the backward section of the wave is reflected by the nearest venous dam and thus adds itself to the forward wave. This explains why an increase of right atrial pressure, produced by local infusion of fluid, is transmitted to the left atrium while a similar infusion in the left atrium usually has no effect on the right atrium.

From a purely physiologic point of view, it is apparent that the backward waves, produced by atrial contraction, are reflected by the nearest venous dam and reinforce the effect of atrial contraction on the ventricles The fact that while the subject is in the supine decubitus, venous pulsations can be observed in the jugular veins shows that the venous collapse at the thoracic entrance is imperfect and can be overcome by the peaks of the atrial waves; this is similar to the case of high waves moving upstream which reach over and pass a dam across a river. Obviously, this phenomenon is more marked in expiration, when the downstream dam of the venous bed is higher (Fig. 2-69).

It results from the above that the following *causes may produce variations of venous return* and cardiac output: (1) inspiratory increase of cardiac work; (2) inspiratory reduction of cardiac output, due to elevation of the abdominal and pulmonary dams; (3) greater expiratory impedance, determined by the peaks of the atrial retrograde waves The resultant action of these causes might explain the *inspiratory increase of venous return* (Brecher et al). It is apparent, however, that this possible inspiratory increase does not depend upon a direct action of the pleural aspiration on the venous content. On the contrary, it can be affirmed that in physiologic conditions, *venous return and systemic pressure are protected against respiratory changes of pleural pressure*

Figures 2-65 and 2-69 also demonstrate that

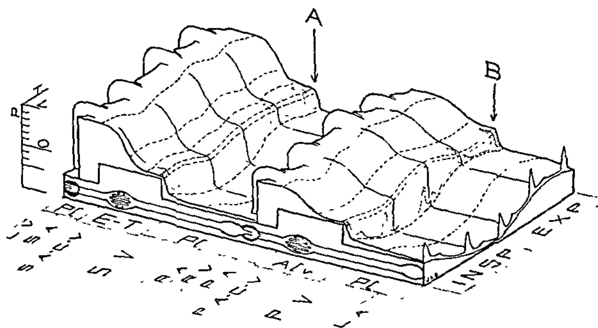


Fig. 2-69. Variations of the hydraulic gradient (H G) of the circulatory system as a function of time (with no proportionality) Each point of the H G. marks a vascular or intracavitary pressure. A, Waterfall from the abdominal "zero" level to the pleural level, B, waterfall from the alveolar or intrapulmonary level to the pleural level Retrograde atrial waves are projected on both waterfalls P, L, T, Pressure, length, time, O, cardiac level Other letters indicate the different media, as in Fig 2-65, the different segments of the cardiovascular system, and the respiratory periods.

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When the collapses disappear, the circulatory system becomes a continuous system of tubing. It is then possible for inspiration to facilitate the venous return and for expiration to enhance cardiac systole; it is even possible that blood can be brought to circulate by the action of respiratory activity alone, as occurs in the classical model of Landois.

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The venous system

Physiology of the Veins

A. D. M. GREENFIELD

Pulsations of the Large Veins

ALDO A. LUISADA AND A. BARBOSO LIMA

PHYSIOLOGY OF THE VEINS

For comprehensive reviews of the physiology of the veins see Gollwitzer-Meier (1932), Franklin (1937), and Landis and Hortenstine (1950).

STRUCTURE OF THE VEINS

The main component of the vein walls is collagen fibers In veins which undergo functional changes in length, these fibers are largely arranged spirally. Associated are varying amounts of elastic and of smooth muscle fibers The functional significance of this structure is reviewed by Burton (1954) The veins of the lower extremity have much more *muscle* and *elastic tissue* than those of the upper Normal veins have a great reserve of strength, and in acute experiments the bursting pressure is about 7 atmospheres.

There are no *valves* in the venae cavae, the cerebral, hepatic, portal, and pulmonary veins, or the superficial veins in the head and neck. Valves are numerous in the veins of the limbs, more so in the leg than in the arm and more so in the deep than in the superficial veins When competent, they can withstand pressures of up to about 3 atmospheres, but they may become incompetent if the vein is dilated

Valves are of greatest importance in the legs. The common iliac vein occasionally has a valve, but it is usually incompetent Twenty-four per cent of external iliac veins have a valve, and 66 per cent of these are competent The femoral vein usually has three valves, but occasionally none or as many as six. More than 66 per cent of femoral veins have a valve at the upper end, and almost all of them are within 1 cm of the inguinal ligament; 90 per cent of femoral veins have a valve just below the mouth of the profunda tributary. There are about 12 valves in the great and small saphenous veins, and in most of the communicating veins above the ankle there are valves permitting blood to flow from the superficial to the deep system.

MEASUREMENT OF VENOUS PRESSURE

Direct observations are made by inserting into the vein a needle connected to a saline (Moritz and Tabora, 1910, Burch, 1951) or other form of manometer In superficial veins above the level of the heart, such as the external jugular, the pressure is approximately atmospheric at the meeting of the collapsed and filled portions. In distended superficial veins the pressure can be indirectly measured as the pressure in a capsule which just causes collapse.

The pressure may be expressed as the vertical height of the meniscus in the saline manometer above either (1) the vein or (2) a horizontal plane through the heart A convenient plane is the *phlebostatic level* (Burch, 1951) In the vertical subject, this coincides with the transverse plane through the sternum at the level of the fourth intercostal space In the supine subject, it coincides with the midfrontal plane, halfway between the front and back of the chest In the reclining sub-

ject, it passes through the *phlebostatic axis*, the line of intersection of the transverse and midfrontal planes

PRESSURE IN THE VEINS

The pressure at the downstream discharge point of the systemic venous system is the pressure in the right atrium; this pressure is primarily determined by the action of the heart. *In the horizontal position*, the pressure at any point "upstream" in the venous system exceeds this pressure by an amount depending on the volume flow and resistance to flow of blood *in the veins* between that point and the heart.

Stated another way, the blood sets out from the heart at aortic pressure and arrives back at right atrial pressure, the pressure in a peripheral vein is at a point between these extremes, depending on the ratio of the resistance to flow from the aorta to the vein, and from the vein to the atrium The former resistance is so much larger than the latter that *the venous pressure is closely related to the atrial, and almost independent of the aortic pressure* [3]

The resistance to flow in the veins is so small that the decrease in pressure from the foot to the groin amounts to only about 80 mm water or 6 mm Hg (Ochsner et al, 1951), from the arm to the right atrium it ranges from 12 to 76 (average 39) mm water (Richards et al, 1942) The pressure in the peripheral veins is little altered even when there are considerable variations in volume flow, the local peripheral resistance may change considerably without much change of the ratio of upstream to downstream resistance Thus, there is no increase in the pressure in the basilic vein during reflex vasodilatation, and only a small drop during reflex vasoconstriction and on arresting the return of blood from distal parts The volume flow from a large arteriovenous anastomosis, however, may considerably increase the local venous pressure (Kennedy and Burwell, 1944), although the atrial pressure may be normal

The venous pressure is greatly increased by obstruction downstream, whether by kinking, compression, or obliteration of the lumen The pressure then rises at a rate determined by the arterial inflow to the territory of drainage, the distensibility of the vessels, and the resistance offered by any alternative venous drainage pathway. *The final level of venous pressure depends on the resistance of alternative channels, and comes to equal the mean arterial pressure if there are none, it is unrelated to right atrial pressure.*

A sustained rise in right atrial pressure or impedance to the return of venous blood to the heart leads to a rise in pressure throughout the venous system This is seen during positive-pressure breathing On the other hand, transient increases in central venous pressure, e.g., during the Valsalva maneuver, coughing, and straining, are transmitted through the venous system only as far as the first effective valves, and they are transmitted with least decrement *in those veins* already distended with blood. Beyond the valves, the rate of rise of venous pressure depends on the rate of filling from the periphery (Sharpey-Schafer, 1955). The collapsibility of the veins limits the fall in peripheral venous pressure during negative-pressure breathing.

EFFECTS OF POSTURE ON VENOUS PRESSURE

On rising from the lying position, venous pressures become modified by the action of gravity on the blood columns The pressure in the right atrium is still set by the action of the heart A horizontal plane may be imagined through the level of blood in a vertical tube connected to the right atrium (Fig 2-70). *Broadly, veins above this plane, including the superior vena cava* (Duomarco et al, 1950), *are partly collapsed* Their collapse prevents the pressure falling to the subatmospheric levels that would be found in rigid tubes in this position, and the pressure within them is just in excess of the local tissue pressure. In most places the local tissue pressure is just above atmospheric, in the skull, however, both the tissue (intracranial) pressure and the venous pressure may fall below atmospheric, the rigidity of the skull enabling the cerebral circulation to act as a siphon, and so affording some protection against the action of gravity.

Veins below the plane are in general distended. If they were insert tubes, the pressure in them would be expected to support a static column of blood extending a little higher than the column supported by the right atrium In the relaxed subject, the pressure is generally only a little less than expected. Similarly, in

[3] Further details have been presented in Chap. 19 *Editor*

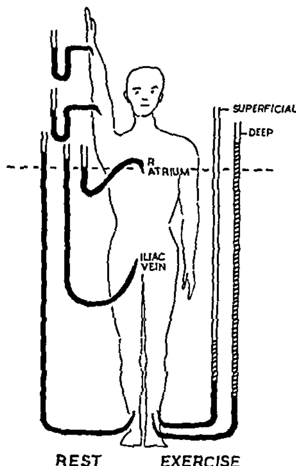


Fig. 2-70. Left, relaxed subject is tilted to the near vertical position, and venous pressure is indicated by water manometers. Right, walking subject; fluctuations in the pressure in deep and superficial veins recorded with high-frequency manometers are for convenience also represented in terms of the levels in water manometers, water manometers are in practice incapable of recording such fluctuations accurately.

a person lying on his side, the pressure in the veins of the under arm hanging through a hole in the couch is sufficient to support a column of water extending 3.4 ± 0.9 cm above that supported by the right atrium, and the difference is sufficiently regular to allow the atrial pressure to be deduced from the measurement on the arm.

THE "MUSCLE PUMP"

The pressure in the superficial veins of the leg is very considerably reduced by exercise of the leg muscles (Smirk, 1936, Beecher, 1937, Pollack et al, 1949a, Walker and Longland, 1950). This is because of the action of the "muscle pump" Contraction of the muscles increases the intramuscular pressure, particularly in the deeper muscles surrounded by nondistensible fascia, and squeezes blood from the deep veins which (in the normal but not in the postphlebitic veins) is compelled by the action of the valves to move centrally. The pressure in the veins is increased during contraction but decreased following the subsequent relaxation of the muscles While the pressure is thus decreased, blood from the superficial veins passes by the communicating veins into the deep veins, and provided the valves in the superficial veins are competent (Pollack et al., 1949a, Warren et al, 1942), the pressure in them is reduced. The reduction, which may amount to more than 60 mm Hg at the foot, depends on the severity of the exercise. It is also much greater in cold subjects (with a small limb blood flow) than in hot subjects (with a large limb blood flow).

The limit to the reduction in pressure in the superficial veins is set, not by the mean pressure, but by the lowest pressure in the deep veins. During modest exercise (Hojensgard and Stürup, 1953), the mean pressure is more greatly reduced in the (superficial) long saphenous vein (60 cm water) than in the (deep) posterior tibial vein (40 cm water), and is not reduced at all in the popliteal vein. Drainage of blood from superficial to deep veins ceases to be an apparent anomaly when it is remembered that the mean pressure in the ventricles of the heart greatly exceeds that in the veins and atria from which they pump the blood The passage from superficial to deep veins has been confirmed by x-ray studies.

It will be noted that during exercise, the reduction in venous pressure in the normal leg increases the arteriovenous pressure difference very considerably, and so helps to increase the blood flow

THE RETURN OF VENOUS BLOOD TO THE HEART

Although the ventricles in diastole exhibit a slight elastic recoil, this suction cannot be transmitted through the collapsible atrium and veins (Brecher, 1956a) Filling of the heart depends on delivery to it of blood at a pressure in excess of the intrapericardial pressure. The intrapericardial pressure does not normally differ from the local intrapleural pressure, and the mean value is slightly subatmospheric The increasing rigidity of the lungs as they are inflated may, however, cause inequalities in

intrapleural pressure in different regions, and relatively increase this pressure near the heart. Because of the difference in the densities of lung and blood, the diastolic transmural pressure varies with the level of measurement, and is more favorable for cardiac filling at lower than at higher levels.

In the horizontal position, the energy for the return of venous blood is derived mainly from the heart, the residual potential energy supplied by the heart's contraction providing a sufficient gradient of pressure along the veins. In the vertical position, the energy is supplied mainly by the heart in the head, neck, and trunk, and mainly by the muscle pump in the limbs. The abdominal viscera, supported by the abdominal wall, may be thought of as a fluid medium surrounding the abdominal vessels and having a density near that of blood (Duomarco et al, 1944). Under the action of gravity, the viscera apply counterpressure which about balances that set up in the valveless abdominal veins, and so prevent gravitational pooling of blood. The visceral circulation has a natural anti-g tendency. Current opinion is that voluntary muscle tone, as opposed to contraction, is of minor importance in promoting venous return (Wiggers, 1950b).

Inspiration draws blood as well as air into the thorax, the blood being aspirated from filled lengths of extrathoracic veins which act as collapsible reservoirs (Brecher et al, 1952). Blood is *not* aspirated from more distant veins because of venous collapse. Expiration acts in the reverse sense, but the net effect of respiratory movements is to assist the venous return and to reduce the amount of blood held in the large veins. The velocity of flow towards the heart in the superior vena cava is speeded during ventricular systole (Brecher, 1954), partly because of downward movement of the AV ring, and partly because ventricular systole discharges blood from the thorax and lowers intrathoracic and venous pressures. The effect of various types of artificial respiration on venous return is described by Brecher (1956b).

BLOOD RESERVOIRS

In man, blood storage in, and mobilization from, stagnant backwaters is unimportant. In cats and dogs, the spleen discharges blood rich in red cells in response to exercise, hemorrhage, and other stimuli (Barcroft et al, 1925), but in man the reactions of normal and splenectomized individuals to exercise, epinephrine, and blood loss are indistinguishable (Ebert and Stead, 1941).

In most parts of the body, however, the vessels, and particularly the veins and venules, may at times be distended with extra blood, surplus to that required for their efficient irrigation and having no local metabolic value. *To this extent, the vessels of most parts of the body may be said to have a reservoir function. This function is unequally developed in different organs, it is pronounced in the pulmonary vessels and is perhaps above average in the liver.* Blood "stored" in such reservoirs is part of the circulating blood volume, in estimations of which it is included, and its composition does not differ from that of other circulating blood. There is some doubt as to whether any appreciable amount of blood traversing the pulmonary circulation in slow pathways may escape inclusion in estimations of central blood volume based on timing the passage of dyes through the lungs. The distribution of the blood volume and interreservoir shifts of blood were reviewed by Sjostrand (1953).

The most important reservoir vessels are the veins. In vitro, the pressure-volume curve of veins shows a zone of free distensibility, corresponding to the change from the collapsed to the filled state, in which a slight increase in pressure causes a large increase in volume. There follows a zone of elastic stretch, in which volume increase depends on stretching of the walls and requires a considerable increase in pressure (Ryder et al., 1944). The stretch is eventually limited by nonelastic elements in the walls. In vivo, these phases become rather blurred when the pressure-volume curve of the whole forearm vasculature is considered (Fig. 2-71). From post-mortem measurements of the dog's mesenteric vessels it is calculated (Landis and Hortenstein, 1950) that *74 per cent of the blood is in the veins and venules*, 6 per cent in the capillaries, and 20 per cent in the arteries and arterioles. These proportions cannot be measured exactly in the living person, but observations of the effects on the limbs of external pressure and venous congestion show that the capacity of the low-pressure vessels is both large and variable. A venous congestion of 30 mm Hg doubles the volume of blood in the forearm held vertically at heart level. An

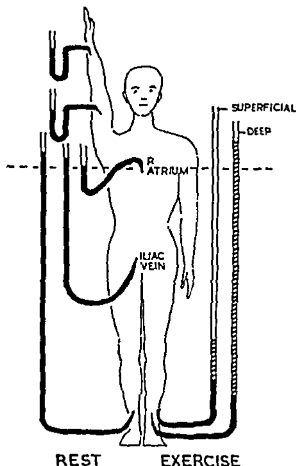


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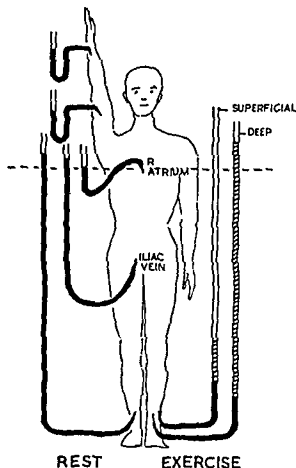


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The limit to the reduction in pressure in the superficial veins is set, not by the mean pressure, but by the lowest pressure in the deep veins. During modest exercise (Höjensgard and Stürup, 1953), the mean pressure is more greatly reduced in the (superficial) long saphenous vein (60 cm water) than in the (deep) posterior tibial vein (40 cm water), and is not reduced at all in the popliteal vein. Drainage of blood from superficial to deep veins ceases to be an apparent anomaly when it is remembered that the mean pressure in the ventricles of the heart greatly exceeds that in the veins and atria from which they pump the blood. The passage from superficial to deep *veins has been confirmed by x-ray* studies

It will be noted that during exercise, the reduction in venous pressure in the normal leg increases the arteriovenous pressure difference very considerably, and so helps to increase the blood flow

THE RETURN OF VENOUS BLOOD TO THE HEART

Although the ventricles in diastole exhibit a slight elastic recoil, this suction cannot be transmitted through the collapsible atrium and veins (Brecher, 1956a) Filling of the heart depends on delivery to it of blood at a pressure in excess of the intrapericardial pressure. *The* intrapericardial pressure does not normally differ from the local intrapleural pressure, and the mean value is slightly subatmospheric The *increasing rigidity of the* lungs as they are inflated may, however, cause inequalities in

intrapleural pressure in different regions, and relatively increase this pressure near the heart. Because of the difference in the densities of lung and blood, the diastolic transmural pressure varies with the level of measurement, and is more favorable for cardiac filling at lower than at higher levels.

In the horizontal position, the energy for the return of venous blood is derived mainly from the heart, the residual potential energy supplied by the heart's contraction providing a sufficient gradient of pressure along the veins In the vertical position, the energy is supplied mainly by the heart in the head, neck, and trunk, and mainly by the muscle pump in the limbs The abdominal viscera, supported by the abdominal wall, may be thought of as a fluid medium surrounding the abdominal vessels and having a density near that of blood (Duomarco et al, 1944). Under the action of gravity, the viscera apply counterpressure which about balances that set up in the valveless abdominal veins, and so prevent gravitational pooling of blood The visceral circulation has a natural anti-g tendency Current opinion is that voluntary muscle tone, as opposed to contraction, is of minor importance in promoting venous return (Wiggers, 1950b)

Inspiration draws blood as well as air into the thorax, the blood being aspirated from filled lengths of extrathoracic veins which act as collapsible reservoirs (Brecher et al, 1952) Blood is not aspirated from more distant veins because of venous collapse Expiration acts in the reverse sense, but the net effect of respiratory movements is to assist the venous return and to reduce the amount of blood held in the large veins The velocity of flow towards the heart in the superior vena cava is speeded during ventricular systole (Brecher, 1954), partly because of downward movement of the AV ring, and partly because ventricular systole discharges blood from the thorax and lowers intrathoracic and venous pressures The effect of various types of artificial respiration on venous return is described by Brecher (1956b)

BLOOD RESERVOIRS

In man, blood storage in, and mobilization from, stagnant backwaters is unimportant In cats and dogs, the spleen discharges blood rich in red cells in response to exercise, hemorrhage, and other stimuli (Barcroft et al, 1925), but in man the reactions of normal and splenectomized individuals to exercise, epinephrine, and blood loss are indistinguishable (Ebert and Stead, 1941).

In most parts of the body, however, the vessels, and particularly the veins and venules, may at times be distended with extra blood, surplus to that required for their efficient irrigation and having no local metabolic value. *To this extent, the vessels of most parts of the body may be said to have a reservoir function. This function is unequally developed in different organs; it is pronounced in the pulmonary vessels and is perhaps above average in the liver* Blood "stored" in such reservoirs is part of the circulating blood volume, in estimations of which it is included, and its composition does not differ from that of other circulating blood. There is some doubt as to whether any appreciable amount of blood traversing the pulmonary circulation in slow pathways may escape inclusion in estimations of central blood volume based on timing the passage of dyes through the lungs. The distribution of the blood volume and interreservoir shifts of blood were reviewed by Sjostrand (1953)

The most important reservoir vessels are the veins In vitro, the pressure-volume curve of veins shows a zone of free distensibility, corresponding to the change from the collapsed to the filled state, in which a slight increase in pressure causes a large increase in volume. There follows a zone of elastic stretch, in which volume increase depends on stretching of the walls and requires a considerable increase in pressure (Ryder et al, 1944) The stretch is eventually limited by nonelastic elements in the walls In vivo, these phases become rather blurred when the pressure-volume curve of the whole forearm vasculature is considered (Fig. 2-71) From post-mortem measurements of the dog's mesenteric vessels it is calculated (Landis and Hortenstein, 1950) that *74 per cent of the blood is in the veins and venules*, 6 per cent in the capillaries, and 20 per cent in the arteries and arterioles These proportions cannot be measured exactly in the living person, but observations of the effects on the limbs of external pressure and venous congestion show that the capacity of the low-pressure vessels is both large and variable A venous congestion of 30 mm Hg doubles the volume of blood in the forearm held vertically at heart level An

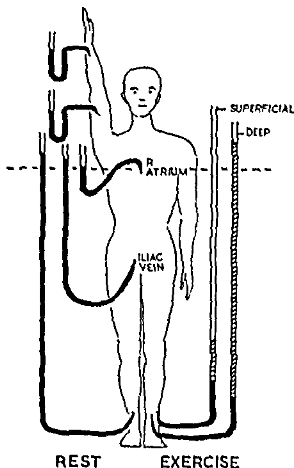


Fig. 2-70. Left, relaxed subject is tilted to the near vertical position, and venous pressure is indicated by water manometers. Right, walking subject; fluctuations in the pressure in deep and superficial veins recorded with high frequency manometers are for convenience also represented in terms of the levels in water manometers; water manometers are in practice incapable of recording such fluctuations accurately.

a person lying on his side, the pressure in the veins of the under arm hanging through a hole in the couch is sufficient to support a column of water extending 3.4 ± 0.9 cm above that supported by the right atrium, and the difference is sufficiently regular to allow the atrial pressure to be deduced from the measurement on the arm.

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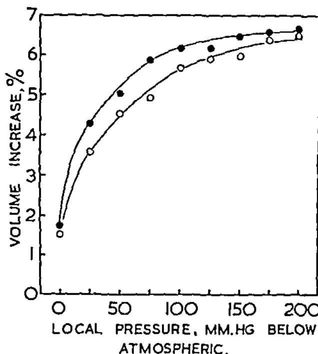


Fig. 2-71. Pressure-volume curves of the forearms of two comfortably warm subjects. The reference volume is that of the forearm emptied of easily mobilizable blood by exposing the arm to a pressure 200 mm Hg above atmospheric. The vessels were distended by exposing the arm to various pressures below atmospheric *(From Greenfield and Patterson, 1956)*

extra 40 ml blood in the arterial system of the average man raises the pressure by about 40 mm Hg, but in the venous system only by about 0.2 mm Hg, thus, the venous system is very much more easily distended than the arterial.

Substantial *redistributions of blood* follow changes in posture and other stimuli. For example, of the total blood volume, the legs contain 13 5 per cent with the subject horizontal; 20.5 per cent with head tilted 60° up, 12 per cent with head tilted 60° down, 16 per cent when standing freely, and 25 5 per cent while standing ½ min after working On lying after standing, 600 ml blood may leave the legs (Sjostrand, 1952) While standing, the amount of blood in the legs depends on how well the muscle pump keeps up with the arterial inflow Pooling in the legs may cause arterial hypotension in one-half and syncope in one-quarter of healthy young men when, following exhausting exercise, they are passively tilted to the 70° foot-down position, moving the legs restores the arterial pressure and prevents fainting. Some healthy men faint on standing quietly after running to exhaustion, or on standing in the lordotic posture, in which the inferior vena cava is obstructed at the diaphragm. The considerable pooling in varicose veins may embarrass the circulation on standing Pooling in the legs is prevented by standing in water up to the level of the heart

Of 600 ml blood leaving the legs on lying down, about 60 per cent goes to the lungs and about 20 per cent elsewhere in the thorax (Sjostrand, 1952). Similarly, *about half the blood lost in hemorrhage is believed to come from the pulmonary circulation* (Glaser and McMichael, 1940). Thus, the changes in pulmonary blood volume are very large in proportion to the normal resting volume.

The hepatic veins of dogs are capable of contraction which may greatly alter the blood content of the liver and portal system (Bauer et al., 1932, Thomas et al, 1949), and the liver is an important blood reservoir in the cat. In man, blood may be displaced from the liver, particularly in cases of congestive failure, by pressure over the abdomen, and the radiographic shadow of the liver is decreased by hemorrhage, but it is not clear whether the reservoir function is especially well developed

VENOMOTOR NERVES AND REFLEXES

Since the capacity of the veins is such a large fraction of that of the vasculature as a whole, alterations in venous distensibility are of great importance. Unfortunately, knowledge of this subject, particularly in man, is fragmentary.

In animal experiments, Donegan (1921) showed that the mesenteric and peripheral superficial veins are able to contract in response to direct irritation and to stimulation of their sympathetic nerve supply The mesenteric veins responded reflexly to stimulation of afferent nerves The splanchnic veins participate in pressor reflexes, reflexly relax on distention of the inferior vena cava, and reflexly constrict after hemorrhage (Alexander, 1951, 1955, 1956) Electrical stimulation of the sympathetic nerves causes a rise in the pressure in the small venules of the hind paw of the dog (Kelly and Visscher, 1956), indicating an increase in resistance downstream from the point of measurement relatively greater than the increase upstream in the arterioles and capillaries The veins of the limbs actively contract in dogs

centrifuged in the feet-out position, and the strength of this response is correlated with the ability of the dog to maintain arterial pressure.

Human veins are capable of powerful contraction when directly irritated, and may obliterate their lumen The superficial veins of the forearm are contracted in the cold subject and relaxed in the warm one In temporarily isolated segments of superficial forearm veins, the pressure rises (indicating an increase in contractile force of the musculature) on inspiring against a resistance, apprehension, placing the opposite hand in ice water, and rebreathing 5 per cent carbon dioxide, these responses are usually abolished by perivenous procain block and ganglionic block and are mediated by the sympathetic nerves Similar increases in pressure during the Valsalva maneuver, exercise, and hyperventilation are smaller than normal in cases of postural hypotension

Thus, human limb veins are undoubtedly capable of active responses The importance of such responses in controlling the distribution of blood in the venous system and the adjustment of circulatory capacity to circulating blood volume is not yet fully evaluated In the limbs, the vasodilatation of the resistance vessels brought about by local or general heating and following exercise is accompanied by very little increase in the distensibility of the total vasculature (Greenfield and Patterson, 1956).

The capacity vessels are presumed to be under the control of the volume receptor mechanism, and venomotor responses to the Valsalva maneuver and the reduction in the distensibility of the hand vessels during positive-pressure breathing are probably examples of such a reaction. The near constancy of the central venous pressure during moderate hemorrhage and transfusion (0 7 cm water per 100 ml volume change in the average subject—Gauer et al , 1956) may also be partly due to a reflex relaxation of the capacity vessels, but this has not been demonstrated to be so

AFFERENT NERVES FROM THE VEINS

The importance of afferent nerves from the peripheral veins in circulatory adjustments is doubtful Lynn and Simeone (1952) were unable to confirm in the dog reflex vasomotor responses to electrical stimulation or distention with irritant fluids of the femoral vein. Greenfield and Patterson (1954) and Roddie (1955) were unable to confirm in man the existence of a venovasomotor reflex by which distention of the veins is alleged to cause local arteriolar vasoconstriction

PULSATIONS OF THE LARGE VEINS

The large veins of mammalians present several pulsations which have been carefully studied on account of the information that they supply in regard to muscular and valvular events of the right heart

Slightly different waves have been recorded over the tributaries of the superior and those of the inferior vena cava The pulsations of the former are either recorded over the *jugular vein* or obtained through catheters passed through this vein into the *superior vena cava*. The pulsations of the latter are studied over the *liver* or through catheterization of the *inferior vena cava*.

Superior Vena Cava The normal tracing shows three positive and three negative waves (Fig 2-72).

A positive wave (A wave) occurs in presystole during and slightly after atrial contraction It is usually rounded but may be tall and peaked A *second positive wave* occurs during the closure of the tricuspid valve (*AV wave*). It is a small wave followed by a long and slow depression (*x*, or *systolic collapse*), which lasts throughout most of the ejection period and slightly beyond it Toward its end, a little notch may mark the closure of the semilunar valves. A *third positive wave* (*V*) occurs in early diastole It is a peaked wave which coincides with the opening of the tricuspid valve and marks, therefore, the beginning of right ventricular filling This is followed by another depression (*y*, or *diastolic collapse*) In indirect tracings recorded over the jugular bulb (Fig. 2-73), another wave is visible. This is the *C wave*, which coincides with the ejection of blood into the aorta.

It has been shown (Caeiro) that each wave of the venous tracing is the result of changes of volume, pressure, and velocity. The relationship between these three factors varies from moment to moment. Moreover, it is likely

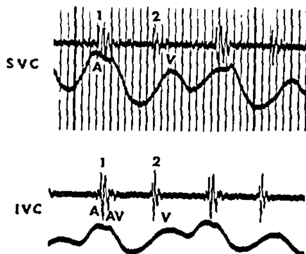


Fig. 2-72. Tracings of pressure within the venae cavae of normal subjects *SVC*, superior vena cava; *IVC*, inferior vena cava. Both tracings show an A wave, an AV wave (unlabeled in top tracing) and a V wave.

that in high venous pressure, changes of pressure predominate over changes of volume, because the veins are already distended

The presystolic A wave is undoubtedly related to the contraction of the right atrium, as shown by its absence in atrial fibrillation Its beginning marks the beginning of atrial contraction; its peak, the end of the same phase. The A wave is largely a *pressure wave* with additional *volume* and *velocity* components. Actual regurgitation of blood from the atrium into the vena cava is minimal in normal subjects but becomes greater when venous pressure is high and the vein is dilated The wave is much larger when simultaneous contraction of the atria and ventricles leads to important regurgitation of blood into the venous system, as in nodal rhythm, nodal premature beats, and AV block The AV wave is due to the results of closure of the tricuspid valve It should coincide with the first part of the first sound However, because of the time of transmission from the valve to the neck, this wave usually coincides with the second part of this sound

The systolic C wave is a *pressure wave* In many cases it is due to transmission of the strong pulsation of the underlying subclavian or carotid artery and thus is an unavoidable artifact. In other cases, the wave is venous and is caused by an arterial pulsation, transmitted from the ascending aorta to the superior vena cava. The same is true of a small notch which marks the closure of the semilunar valves

The early-diastolic V wave is connected with the opening of the tricuspid valve. The rise preceding its peak is the expression of the gradual filling of the right atrium Therefore, the V wave is chiefly a *volume wave* However, as the fall of the curve is caused by the opening of the tricuspid valve, its descending limb is largely due to a *drop in pressure.*

A small depression occurs during early tension of the ventricles. Its depth is greater when the interval between atrial and ventricular contractions is longer. The depression x (systolic collapse), which occurs during systolic ejection, is caused by suction of venous blood due to the outflow of blood from the thorax and by a downward movement of the AV septum It is, therefore, a wave due to increased speed of the blood and decreased volume of the vein.

The depression y (diastolic collapse) follows the V wave and is terminated by slow filling of the right atrium.

There is no constant relation between the waves of the phlebogram and those of the electrocardiogram, except for a close time relationship between the intervals a-c and P-Q.

The main vibration of the second sound precedes the peak of V by about 0 10 sec, while the third sound falls during the descending limb of V, e.g , 0.0064 to 0 0078 sec later. However, there may be a much shorter interval between V and the third sound, and there may even be coincidence. This fact is due either to

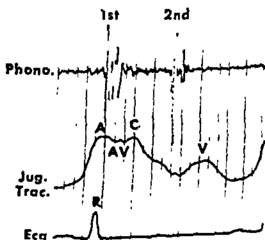


Fig. 2-73. Jugular tracing of a normal subject recorded together with a phonocardiogram and an electrocardiogram. Visible are waves A, AV, C, and V. The notch marking the closure of the semilunar aortic valve (2nd) is also visible

slower transmission of the V wave or to marked delay in right ventricular events in comparison with those of the left heart (which cause the recorded third sound).

Inferior Vena Cava. The pulsations of the inferior vena cava can be studied by means of catheterization (Fig. 2-72)

The waves of the jugular and hepatic tracings practically coincide, except for the C wave, which is absent in the latter A small notch (AV wave) separates the A wave from the systolic collapse It is due to closure of the tricuspid valve and is similar to that occurring within the right atrium

The fourth (atrial) sound slightly precedes the peak of the A wave of the venous tracing This coincidence is due to the fact that both events follow the atrial contraction; the fourth sound is due to the blood hitting the ventricular wall, while it takes some time for the transmission of the A wave from the right atrium to the vein The descending limb of the A wave is so slow that it ends after the start of the first sound.

I

Blood flow through muscle and skin in man

CHESTER HYMAN

Knowledge of the blood flow through the muscles and skin of the normal human being is based almost entirely on analyses of the situation in the extremities (Abramson, 1944, Barcroft, 1956) Technical difficulties have thus far prevented the accumulation of data on any except these parts Although great quantitative and qualitative variability may be encountered in other areas, it is permissible to generalize from the data so far available, since most of the skeletal muscle and much of the skin are found in the extremities

The total mass of tissue is more than half the body weight skin comprises about 6 per cent of the total, and skeletal muscle about 50 per cent About 25 to 30 per cent of the cardiac output flows through these tissues, but since this flow can be acutely and drastically altered, it can suddenly throw embarrassingly large demands on the circulatory system Resting muscle has a basal flow of about 4 ml/100 ml muscle per minute, during exercise this may increase to 50 ml/100 ml muscle per minute Potentially, 17 5 liters of blood could be diverted through this tissue each minute The blood flow through the skin of the fingertip can fluctuate from about 0 2 ml/100 ml/min to almost 120 ml/100 ml/min (Wilkins et al, 1938) Although this is higher than the blood flow encountered in other areas, dilatation of *all* the skin vessels would, nevertheless, require an almost intolerable fraction of the cardiac output These maximal skin blood-flow demands are rarely developed simultaneously

Circulation through skin and muscle subserves two general requirements: it supplies the metabolic needs of that tissue, increasing as the activity of the tissue increases; and it fulfills a more general physiologic need by participating in a variety of reflexes. In skin, blood flow is principally modified by factors of the second type, i e, those associated with general bodily requirements, whereas the local metabolic shifts are of greater significance in the case of muscle. The vascular effects of alterations *in activity* of muscle are profound and easily demonstrated (Barcroft et al., 1952), while local needs in skin can be increased only by thermal increases in metabolism or by activation of the sweat glands—variations which are not clearly established In contrast, the blood flow through skin is varied widely by reflexes which determine body heat storage. Only minor reflex adjustments, in relation to changes in pressure and "filling" of the cardiovascular system, have thus far been demonstrated in skeletal muscle perfusion (Roddie and Shepherd, 1956).

Blood flow through skin and through muscle is determined primarily by the vascular resistance It is generally agreed that this is modified by changes in caliber of the arterioles, accomplished by the smooth muscles in their walls (Burton, 1954) The degree of contraction of this musculature and the factors which can modify it constitute the subject matter of this discussion Although many different physiologic situations may have vasomotor effects,

there are only a limited number of stimuli to which the blood vessels themselves may respond. The end vasomotor mechanisms which pertain to skin and skeletal muscle will be examined

METHODS OF MEASUREMENT

Only a few methods have proved useful in the accumulation of quantitative information about the blood flow through skin and muscle. Direct and microscopic observations of the body surface can give a general picture of the blood flow through skin only The work of Lewis (1927), which combines simple surface temperature measurements with these observations, was extremely fruitful Hertzman et al (1948), using the photoelectric plethysmograph, extended this approach to yield semiquantitative data A related method, the measurement of heat loss per unit area of skin, has given data which, though difficult to interpret, are nonetheless valuable (Greenfield et al, 1950)

The bulk of the quantitative information about peripheral blood flow has come from the application of the plethysmographic technique The venous occlusion plethysmograph has given much data about the blood flow through the finger, toe, hand, foot, forearm, and calf Ingenious combinations of these data with data obtained by a variety of ancillary techniques have been used to estimate blood flow in the skin or muscle of these parts Though the interpretation of such experiments may require revision, the data obtained are undoubtedly valid (Barcroft and Swan 1953)

Hensel and Ruef (1954) described the *Calorimetersonde*, which measures the rate at which locally introduced heat is dissipated to estimate total blood flow through localized areas Semiquantitative data of skin and muscle circulation have been acquired in this way Andres *et al* (1954) have extended the dye-dilution technique to the measurement of blood flow in human extremities The exchange of solutes between the blood and the tissues has been estimated by two techniques Kety's (1949) *tissue-clearance method*, and the simultaneous measurement of two intraarterially injected labels, described by Freis et al (1953) These techniques give an index of the efficacy of tissue perfusion rather than a measure of total blood flow

REGULATION OF BLOOD FLOW IN SKIN AND MUSCLE

All the stimuli which are thought to be capable of altering arteriolar caliber may be conveniently grouped into four categories: (1) factors resulting from tissue activity, (2) humoral agents, (3) nervous impulses; (4) physical changes. For most physiologic responses, it is difficult to identify the actual stimulus to the vascular smooth muscle, in fact, a single uncomplicated stimulus can rarely be demonstrated except in special laboratory experiments However, in the interests of clarity, this system of classification will be adopted below.

Since there is evidence for qualitative differences in the reactivity of the arterioles in different tissues, the responses of skin and of muscle blood vessels will be discussed separately. Almost all information about muscle circulation is derived from measurements on forearm and calf blood flows, where qualitative similarities in the data encourage generalization concerning all skeletal muscle. However, the distinct differences between regulation of blood flow through the skin of the fingertip and the forearm make it necessary to discuss these two cutaneous regions separately.

Metabolic Regulation. The alterations in local blood flow associated with increased activity, or subsequent to a period of restricted blood flow, suggest the action of locally produced metabolites in the modification of vascular resistance Barcroft and Millen (1938) showed that the increase in blood flow through muscle during and following exercise is roughly proportional to the work load Mechanical factors may supervene to prevent perfusion of this tissue during a period of sustained contraction, yet evidence for a relaxation of vascular tone can be obtained During rhythmic activity of muscle, a hyperemia can always be demonstrated (Barcroft and Dornhorst, 1954). Hilton (1953) has reviewed the evidence which proves conclusively that this vascular response is associated with the process of contraction.

That some chemical agent was involved in this vasodilatation was shown by the experiments of Anrep and Saalfeld (1935). However, the responsible factor has not as yet been identified. Many of the metabolic resultants of contraction have demonstrable vasodilator effects, but neither oxygen lack, diminished pH, altered P_{CO_2}, increased lactic acid concentration, nor an increase in histamine production can be solely responsible for the changes found in exercise There remains a possibility that acetylcholine, ATP, or potassium ions acting alone, or some combination of these factors, may be the actual stimulus to dilatation (Barcroft, 1956)

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CHESTER HYMAN

Knowledge of the blood flow through the muscles and skin of the normal human being is based almost entirely on analyses of the situation in the extremities (Abramson, 1944, Barcroft, 1956). Technical difficulties have thus far prevented the accumulation of data on any except these parts. Although great quantitative and qualitative variability may be encountered in other areas, it is permissible to generalize from the data so far available since most of the skeletal muscle and much of the skin are found in the extremities.

The total mass of tissue is more than half the body weight: skin comprises about 6 per cent of the total and skeletal muscle about 50 per cent. About 25 to 30 per cent of the cardiac output flows through these tissues, but since this flow can be acutely and drastically altered it can suddenly throw embarrassingly large demands on the circulatory system. Resting muscle has a basal flow of about 4 ml/100 ml muscle per minute; during exercise this may increase to 50 ml/100 ml muscle per minute. Potentially, 17.5 liters of blood could be diverted through this tissue each minute. The blood flow through the skin of the fingertip can fluctuate from about 0.2 ml/100 ml/min to almost 120 ml/100 ml/min (Wilkins et al., 1938). Although this is higher than the blood flow encountered in other areas, dilatation of *all* the skin vessels would, nevertheless, require an almost intolerable fraction of the cardiac output. These maximal skin blood-flow demands are rarely developed simultaneously.

Circulation through skin and muscle subserves two general requirements: it supplies the metabolic needs of that tissue, increasing as the activity of the tissue increases, and it fulfills a more general physiologic need by participating in a variety of reflexes. In skin, blood flow is principally modified by factors of the second type, i.e., those associated with general bodily requirements, whereas the local metabolic shifts are of greater significance in the case of muscle. The vascular effects of alterations *in activity* of muscle are profound and easily demonstrated (Barcroft et al., 1952), while local needs in skin can be increased only by thermal increases in metabolism or by activation of the sweat glands—variations which are not clearly established. In contrast, the blood flow through skin is varied widely by reflexes which determine body heat storage. Only minor reflex adjustments, in relation to changes in pressure and "filling" of the cardiovascular system, have thus far been demonstrated in skeletal muscle perfusion (Roddie and Shepherd, 1956).

Blood flow through skin and through muscle is determined primarily by the vascular resistance. It is generally agreed that this is modified by changes in caliber of the arterioles, accomplished by the smooth muscles in their walls (Burton, 1954). The degree of contraction of this musculature and the factors which can modify it constitute the subject matter of this discussion. Although many different physiologic situations may have vasomotor effects,

constricts the vessels responsible for resistance to flow and dilates the vessels responsible for color in the skin The effects on the blood vessels of muscle are not so clearly elucidated.

Nervous Factors. The principal vasomotor innervation of skin and skeletal muscle is derived from the sympathetic division of the autonomic nervous system Recent analyses of the way in which these factors appear to alter peripheral blood flow have been presented by Barcroft and Swan (1953) and by Folkow (1955). Essentially, one is interested in determining the extent to which smooth muscle is under tonic constrictor tone, in the possibility that such vasoconstrictor fibers, where they exist, can be activated to cause increased vascular tone, and in whether or not there exists a separate set of fibers capable of producing an active vasodilatation (Uvnas, 1954). Briefly, most recent evidence would indicate that in *muscle*, there is a basal, effective sympathetic vasoconstrictor tone which maintains the blood flow at about half the level which may be achieved in the absence of a sympathetic supply This tissue also has an independent set of sympathetic dilator fibers which are not tonically active. This active vasodilatation can be clearly demonstrated by the sudden increase in blood flow through the forearm during *fainting*, when the blood pressure drops to extremely low levels and the skin of the forearm, as well as that of the hand, appears to be blanched. This vasodilatation does not develop in the sympathectomized forearm More recently, Roddie and Shepherd (1956) showed that certain postural changes induce a vasodilatation in muscle via the sympathetic nerves

It is generally agreed that the *skin* of the *hands* and *feet* is generously supplied with vasoconstrictor fibers Section of the sympathetic nervous supply to these tissues results in a manifold increase in the blood flow (Lynn and Barcroft, 1950) However, the results of the most recent careful experiments have failed to demo[illegible]

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The well-known axon reflex originally described by Lewis has been taken as evidence that branches of somatic sensory fibers (probably pain fibers) can cause vasodilatation in skin This response is probably related to the "antidromic" vasodilatation and occurs under traumatic and pathologic circumstances rather than in any physiologic reflex Axon reflexes can be elicited from skin over all portions of the body, but, with rare exception, they are unknown in muscle.

Physical Factors

1. TEMPERATURE. The blood flow through an extremity depends in part on the local temperature, decreasing to a minimum at about 15°C, and then increasing again at lower temperatures Part of the change can be explained by the direct relation between tissue metabolism and temperature, but there is some evidence of a direct effect of temperature on the smooth muscle coats of the blood vessel walls Lewis (1930) explained the increase in blood flow which occurs below 15°C on the basis of traumatic release of a substance which activated an axon reflex mechanism. However, this explanation has recently been questioned. These effects of temperature on peripheral blood flow are complex and not easily summarized Bazett (1949) points out that at these low temperat[illegible]

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Hilton (1953) has suggested that vasodilatation results from an axon reflex set up by the "metabolite" in some as yet unidentified nervous pathway. The possibility of a local nerve net has been considered, but it is not clearly established.

When the blood flow *to a muscle is occluded*, there is a progressive *relaxation of the resistance of blood vessels which leads to a reactive hyperemia when blood is readmitted.* There are many similarities *between this response* and the vasodilatation *of exercise, e.g.*, both are roughly proportional to the discrepancy between tissue need and blood flow, *and* both may be *produced in sympathectomized* muscles. Whether this *reactive hyperemia* results from the same *chemical substance* responsible for the exertional hyperemia is, however, *not established (Patterson and Whelan, 1955). Reactive hyperemia* can be seen in the *skin of the hand (Lewis, 1927)*, and direct *measurements* of blood flow *through this part after a period of ischemia show increases* (Catchpole et al., 1955).

By analogy to the situation in salivary glands, *Fox and Hilton (1956)* argued that cutaneous *vasodilatation may result* from local formation *of a bradykinin-like* substance *released during* activity by *the sweat glands. Since* sweating is *the only way in which dermal* structures can "*increase their activity*," this *bradykinin-like* mechanism would be the *principal chemical mechanism* available for *vasodilatation in those* portions of the skin which sweat.

Humoral Agents. *The* chief hormones *involved in the regulation of peripheral blood flow would appear to be those of the adrenal* medulla, vasopressin, and angiotensin *(derived from renin).* Though not truly *a hormone*, serotonin (5-OH-tryptamine) *will also be considered* in this *group*.

The effects of epinephrine and *norepinephrine* on flow through muscle have been studied by use of the forearm plethysmograph during direct intraarterial and intravenous infusions. When *epinephrine* is introduced into the vein, there is a transient peak increase in blood flow through the forearm, followed by a fall to a sustained plateau. Intraarterial infusions of smaller doses of epinephrine cause only the transient vasodilatation. Since there is an obvious blanching of the skin in both cases, the increases must represent *vasodilatation in muscle. The pattern is merely* exaggerated in *muscles whose sympathetic nervous* pathways *have been interrupted.* It would thus appear that the transient dilatation results from a direct action of epinephrine on the blood vessels, while the sustained contraction is caused by some secondary humoral agent released by the *circulating epinephrine.*

Norepinephrine, infused intravenously, causes *a sustained increase in forearm muscle blood flow which is dependent on an intact sympathetic nervous supply.* Intraarterial *norepinephrine causes a decrease in forearm* muscle *blood flow. This compound, therefore,* has two contrasting actions—a direct constrictor action and a predominant, indirect, dilator action, *apparently mediated by the sympathetic* nervous *system (Whalen, 1954).*

Intraarterially administered epinephrine and norepinephrine both show vasoconstrictor effects in the *hand*, although norepinephrine is reported to be somewhat more potent. When given intravenously, there is some evidence of an indirect, sympathetically mediated, dilator effect in the hand. The net result of the direct and indirect effects of epinephrine is a slight vasoconstriction in the skin of the hand, whereas the effects of norepinephrine balance each other to give no measurable change. It is generally assumed that skin of the forearm and hand responds alike to these amines.

Intravenous infusion of *vasopressin*, the pressor compound from the posterior pituitary gland, causes an initial transient decrease in the flow through the forearm which is then followed by a sustained increase in flow; this can be demonstrated in the sympathectomized limb as well. In the hand it causes only vasoconstriction. It may be concluded that this compound, like epinephrine, causes vasodilatation in muscle in an indirect fashion, i.e., by *the release of a secondary* vasodilator substance *(Kitchin, 1955).*

The effect of *angiotensin* on blood flow *through* the extremities has been studied by several authors. *According* to Abramson (1944), the effects are quite variable, and it is probable that alterations in resistance to blood flow through the extremities are not part of the pressor response to this drug.

Serotonin (*5-OH-tryptamine*), *a* substance released from clotting *blood and possibly* from certain tissue cells under traumatic conditions,

constricts the vessels responsible for resistance to flow and dilates the vessels responsible for color in the *skin*. The effects on the blood vessels of muscle are not so clearly elucidated.

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2. MECHANICAL FACTORS. Lewis (1930) has produced evidence for the fact that the musculature of the "minute vessels of the skin" can be stimulated to constrict by direct mechanical activation (the white reaction). The minute vessels of the skin, in Lewis's classifica-

tion, include the smallest arterioles. The musculature of these vessels, together with the precapillary sphincters, is probably responsible for the observed effect. The extent to which such factors influence over-all blood flow through the skin cannot be readily assessed, but the sensitivity of this response has been measured quantitatively by di Palma et al. (1941). It has not yet been possible to demonstrate a similar response for the blood vessels in muscle.

A change in the caliber of the vessels following on a period of "stretching" has recently been discussed. An increase in transmural pressure tends to increase the tone of the vessels responsible for resistance, and this altered tone may persist for some time after the transmural pressure has been returned to its initial level. A factor of this kind may play some role in reactive hyperemia.

A DUAL CIRCULATION

It has been known for some time that blood flows through two parallel pathways in the skin. Some blood moves through a system of *capillary loops* and exchanges solutes with the tissue fluid. The remainder of the blood passes through somewhat larger, highly muscular, impermeable vessels, the *arteriovenous anastomoses* (Clark, 1938). This system of anastomoses plays an important role in shunting large volumes of blood through the skin and so cools the body. There is good evidence that these anastomoses are under sympathetic nervous control and that their caliber is adjusted in accordance with the thermal requirements of the body.

That a similar dual circulation also exists in muscle has been suggested. Barcroft and Dornhorst (1951) suggest that a fraction of the blood which perfuses muscle is essentially nutritive and that its volume is determined by local metabolic factors; the remainder of the blood flowing through muscle is nonnutritive and is modified by reflex and humoral mechanisms independent of the local needs of the tissue. Although arteriovenous anastomoses in the skin have been clearly demonstrated by morphologists, the existence of an analogous system of bypasses in muscle is suggested on the basis of functional data only. Zweifach (1949) reported observations which, though not conclusive, nevertheless give some morphologic basis for such an argument. The function of such a bypass system in muscle is unclear. It may participate in adjustments of the blood pressure, providing a shunt of relatively large magnitude where the blood would not be unduly cooled or modified, or it may be that large volumes of blood moving through the bypass vessels can increase muscle temperature somewhat in order to increase the thermodynamic efficiency of this tissue.

SUMMARY

During recent years there have been rapid advances in understanding of the circulation through skin and muscle in the unanesthetized normal human being. Most of the data have come from the application of new quantitative methods. The variability, both quantitative and qualitative, between skin and muscle circulation has been frequently commented upon. It would appear that the circulation through muscle is modified in accordance with local needs, primarily, and only secondarily to participate in general reflexes. On the other hand, blood flow through skin is primarily adjusted according to the needs of the body as a whole. It has also been pointed out that the smooth musculature of the arterioles in the skin and in muscle responds differently to various stimuli. For example, epinephrine releases a secondary humoral agent which profoundly constricts skin blood vessels while it dilates those in muscle. Further, not all the skin shows uniform circulatory responses, and careful distinctions must be made between the central and apical portions. There still remain many unanswered questions. These include the exact mechanism of vasodilatation during muscular contraction, the influence of temperature, the characteristics of reactive hyperemia, and a clarification of the situations in which release of vasoconstrictor tone and active vasodilatation may be confused. The problem of a nonnutritive bypass circulation in muscle, functionally analogous to the arteriovenous anastomoses in skin, requires further examination.

22

Circulation of the gastrointestinal tract; splenic and hepatic circulations

EWALD E. SELKURT

GASTROINTESTINAL SYSTEM

Anatomy

The following is a brief review of the circulatory patterns in the stomach and intestine.

Stomach. Main arterial branches supplying the stomach are the right and left gastric arteries and the right and left gastroepiploic arteries The large arteries divide in passing through the gastric wall to form a main plexus of arteries lying in the submucous layer between the muscular coat and mucosa Anastomoses are large and profuse The submucosal plexus gives rise to a rich vascular network supplying the gastric mucosa From this, spring fine arterioles branching to capillaries which run at right angles to the mucosa, penetrating to the surface (Barlow, Barclay *et al*) Thus, there is a vascular pool with channels capable of bringing blood to the mucosa, and transferring it rapidly to a required point Short-circuiting mechanisms are provided by arteriovenous shunts which are capable of passing glass spheres 200 μ in diameter It has been calculated that these may shunt up to one-twentieth of the blood flow supplied to the stomach (Walder, 1953) However, the mechanism of regulation of these shunts has not yet been worked out

Intestine. The typical pattern of vascular distribution to the intestine is illustrated by the superior mesenteric artery The primary branches show characteristic anastomoses, the *arcades*, which are simplest in the region of the jejunum, where only primary arcades are found In man, they increase in number and complexity (secondary, tertiary, and quaternary arcades) into the ileum (Noer, Ross) In the dog, usually only large primary and secondary arcades are found From the arcades arise numerous *vasa recta*, which proceed directly to the intestine, running in line with the fibers of the circular muscle layer No direct anastomoses occur between the vasa recta in man, but they may occur in the dog. The vasa recta proceed to the gut to form the mural branches, where they anastomose by direct or plexiform anastomoses, and finally go on to join across the antimesenteric border of the intestine, alternating to opposite sides of the bowel as they arborize The arcades serve as a *blood depot* system The profuse anastomotic connections may be significant in relation to the intestinal movements, so that blood supply will not be seriously interfered with by peristaltic movements The numerous anastomoses in the wall permit a separation of 3 to 4 in from the mesentery and are protections against distention of the bowel. Arteriovenous anastomoses have been described in the villi of man and the rabbit, but cannot be demonstrated in the dog (Jacobson et al) The mucosa is supplied from the submucosal vessels sweeping up the sides of the villi The capillary network is immediately subepithelial, while arteries and veins are axial in position in the villus Veins correspond to the arteries in distribution, but generally [illegible]

blood

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muscularis mucosa to large submucosal veins which drain into mesenteric veins supplying the portal vein Terminal branches of the superior mesenteric artery join the inferior mesenteric artery to form the colic arteries The large bowel is comparatively avascular in man There is an imper-

fect arcade system with fewer communications between the vasa recta and fewer connections across the bowel

Innervation; Neurogenic Regulation of Flow

Abundant *constrictor sympathetic fibers* are distributed to the splanchnic area, exerting a tonic control over the vessels and providing possibilities of reflex regulation (Folkow, 1956a). Stimulation of the splanchnic nerve decreases flow, and ganglionic blocking agents (hexamethonium, chlorisondamine dimethochloride, and pentolinium tartrate) increase it. Although both epinephrine and norepinephrine cause reduction in flow, it is more likely that norepinephrine is the chemical mediator.

It has been suggested that *sympathetic vasodilator fibers* are also distributed to the intestine, but at present the evidence is not conclusive. The small vasodilatation produced by splanchnic stimulation after the blockade of vasoconstrictor fibers may be a hemodynamic artifact, since sympatholytic drugs do not generally block the inhibitory action of splanchnic stimulation on the intestinal smooth muscles Their relaxation may decrease intravascular tension and hence increase flow Atropine is without effect on such apparent dilator responses, arguing for the absence of cholinergic fibers However, the absence of specific vasodilator fibers does not eliminate the possibility of dilator reflexes For example, a rise in inferior vena caval pressure has been shown to cause a reflex dilatation of the intestinal veins This reflex appears to be initiated by fibers ascending the vagus nerve and to cause reduction in sympathetic tone to the venous musculature.

Hemodynamic Characteristics

Figure 2-74A shows the relationship of intestinal blood flow in the dog to a wide range of perfusion pressures These experiments were performed in isolated, denervated loops of ileum (Selkurt et al.). The pressure-flow relationship is evidently not linear Flow increases progressively at a faster rate than the increase in perfusion pressure. Two factors contribute to this: a passive increase in vessel caliber as intraluminal pressure is increased, and a decrease in the apparent viscosity of blood (so-called anomalous viscosity) at higher flow velocities in small vessels Flow ceases at about 15 mm Hg pressure, the result of "critical closure" of the vessels To the right in the figure, intestinal vascular resistance (given as P.R.U.—peripheral resistance units) is related to the arteriovenous pressure gradient. It is seen that this is also nonlinear and does not conform with Poiseuille's law. This emphasizes the necessity of interpreting humoral and neurogenic influences on flow on the basis of a control pressure-flow curve, so that proper hemodynamic deductions can be made. Ideally, experimental flow should be related to the control flow at the *same perfusion pressure* to quantitate vasomotor changes To study neurogenic influences, preparations with intact innervation should of course be used. This figure supplies information on the quantitative aspects of intestinal flow in the denervated preparation. However, denervation apparently has small effect on flow, as shown in similar studies in dogs comparing flow in loops with intact innervation, with denervated preparations (Lawson, 1941). Thus flow averaged 36 ml/min/100 Gm in intact dogs, as compared to 42 ml/min in denervated dogs at normal arterial perfusion pressure, suggesting a tonic vasoconstrictor action of the sympathetic nervous system in conformity with the afore-mentioned results of autonomic blocking agents

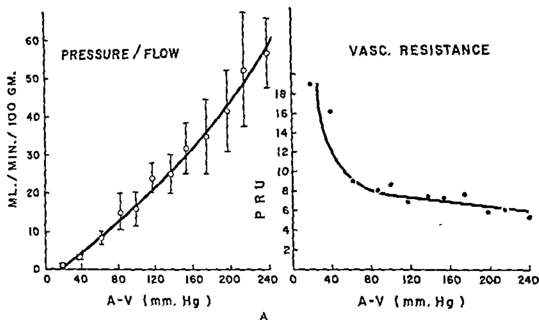
Intestinal Blood Volume

Visceral blood volume in the dog, based upon an exclusion technique utilizing P^{32}, lies between 20 and 50 per cent of total blood volume (Delorme et al.) The average volume was found to be 533 ml, but with a wide scatter. The volume of the mesenteric (intestinal) circuit averaged 56 per cent (range, 24 to 70) of the total splanchnic volumes. The remainder of the splanchnic volume was roughly equally proportioned between the liver and the spleen, with somewhat more in the liver.

Factors Modifying Intestinal Flow

Although further consideration will be given this topic, several areas relating specifically to intestinal blood flow will be considered here

1. Intestinal Distention. The effect of acute distention has been studied in rabbits because of the anatomic similarity of their vascular supply to that of man (Noer et al). Blood flow was observed with the illuminated quartz rod technique during balloon distention. Slowing



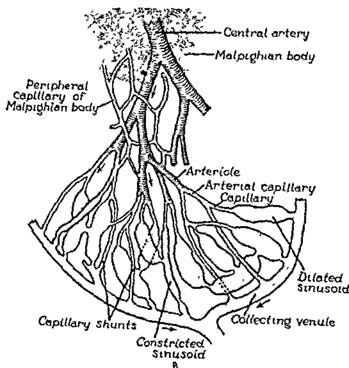


Fig. 2-74 A Relationship of flow (ml/100 Gm) and vascular resistance to perfusion pressure in the isolated intestinal loop (ileum) of the dog Vertical lines through each point are the standard errors of the means of observations made in approximately 20 mm Hg intervals of perfusion pressure (A-V) Results are from 18 experiments To the right, intestinal vascular resistance is given as peripheral resistance units, P.R U, where one P R U = (1 mm Hg)/(1 ml/min), shown in relation to perfusion pressure (*From Selkurt, Scibetta, and Cull*) B Diagrammatic representation of circulation through the spleen (From Peck and Hoerr, 1951.)

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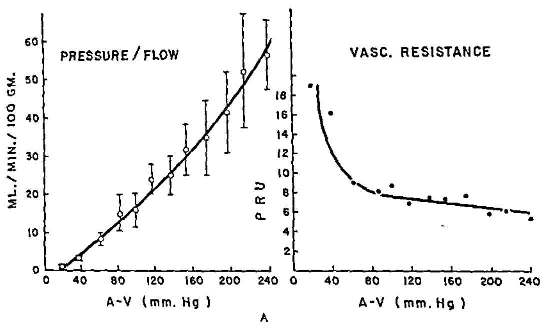
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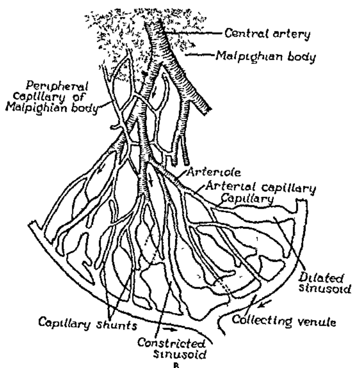


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or stoppage of flow occurred first in venules (at 15 mm Hg pressure), then in small veins (20 mm Hg), then in venous capillaries (30 mm Hg), followed in order by arterioles, small arteries, then arterial capillaries. Flow stopped at 50 to 70 mm Hg, except for slight flow in *mural veins and arteries. Distending pressures* of 30 to 40 mm Hg created disturbances which were completely reversible, but pressures of 50 mm or above produced *irreversible* changes in the mural circulation and intestinal wall, with permanent interruption of flow of many small vessels, interstitial hemorrhage, and pronounced intravascular agglutination of cells. With blockage of veins as the first event, increased capillary pressure causes leakage of plasma into the wall of the gut and into the lumen. If excessive, this will lead to shock, as often occurs with intestinal obstruction. The *seriously impaired arterial circulation at the* higher distending pressures promotes breakdown of the wall of the gut, furthered by proteolytic digestion of tissue, and leads ultimately to gangrene and rupture. Distention of the dog intestine to 30 cm water has been shown to reduce intestinal oxygen consumption, probably basic to these changes (Lawson et al).

2. ***Reflexes; Humoral Mechanisms.*** *Chemoreceptor stimulation (carotid and aortic) by* inhalation of 1 per cent oxygen in nitrogen causes marked reduction in superior mesenteric flow in dogs (Bernthal et al). When Hering's nerves and the vagosympathetic trunks are blocked by narcosis, the reflex is abolished. An interesting relationship between skin temperature and colonic blood flow has been observed (Grayson, 1949, 1951). Using thermoelectric methods, with *thermocouples placed in colostomies*, cecostomies, and ileostomies, or into the rectum, cutaneous cooling (lower extremities) was observed to cause an increase in intestinal flow in excess of a simultaneous increase in blood pressure (cold pressor response), interpreted as active hyperemia. Body heating, causing vasodilatation of the extremities, resulted in vasoconstriction. A *reciprocal interplay of the skin and intestinal blood reservoirs is suggested*, aiding in maintaining the homeostasis of the systemic blood pressure.

Epinephrine and norepinephrine, injected intraarterially, produce vasoconstriction, as do angiotensin and renin (Abell and Page). The author of this chapter has found serotonin to be a constrictor, while ATP, adenylic acid, and adenosine produce hyperemia, as does substance P, a polypeptide which has been isolated from the intestine. Carbon dioxide is a hyperemic agent.

"Reactive hyperemia" of the intestine has *been demonstrated. Complete ischemia* of 2 min or longer produces a marked hyperemia proportional to the duration of the ischemia. Cocaine has no effect in abolishing the response, suggesting a metabolic basis.

SPLEEN

Anatomy

Branches of the splenic *artery course along the* trabeculae of the spleen, passing through the white pulp to break up into arterioles with husklike sheaths (*penicilli*), which constitute the arteriolar stopcocks. These then branch into arterial capillaries, *in turn supplying the sinusoids* (*venous* sinuses), the latter lying in the red pulp of the spleen (Fig. 2-74B). The collecting venules converge ultimately into the splenic vein, which drains into the portal vein. *Sphincters* have been described at the sinusoid outlets which close *during storage* phases. The sinusoids are composed of rodlike "barrel stave" endothelial cells, longitudinally arranged and surrounded by rings or spirals of reticular fibers, reminiscent of barrel hoops, creating a latticelike structure. *The commonly accepted view is that* the system is a closed one (Knisely, Bjorkman) but that the latticework is large enough to permit occasional erythrocytes to slip through. Thus, the sinusoids represent a mechanism creating a "separatory" circulation, filtering off *plasma and* storing red cells in high concentration in the dilated sinusoid, and operating in a cyclic manner. The separated plasma may return through smaller veins and lymphatic vessels to the general circulation. In *a spleen exhibiting a high degree of storage*, constant, rapid flow is seen primarily in the capillary shunts (Fig. 2-74B), which directly connect arterioles with venules. When the splenic capsule contracts under physiologic demand, the concentrated cells are discharged directly into the *portal venous* system. Filtered red cells reenter the venous sinuses by diapedesis, which leads to destruction of fragile erythrocytes. After rupture, the released hemoglobin and stroma are ingested by the reticuloendothelial system *of the spleen, or elsewhere* in the body.

Nervous Regulation

This is achieved by sympathetic outflow in splanchnic nerve branches accompanying *the* artery into the spleen, presumably mediated by

norepinephrine. Regulation is both by way of the smooth muscles of the capsule and trabeculae, and by direct vasomotor action on the arterioles and sphincters Pressures as high as 100 mm Hg can be developed by *splenic contraction* (if the vein is occluded). This contraction, combined with constriction of arterioles, forces the blood out Simultaneous relaxation of the efferent sphincters aids discharge Discharge is evidently initiated by reflex mechanisms, e g , via chemoreceptor stimulation during hypoxia, or pressoreceptor stimulation during hemorrhage Since dilator fibers to the spleen have not been demonstrated, filling is considered to be a passive process, achieved by relaxation of arterioles, by decrease in splanchnic vasomotor tone, and by constriction of efferent sphincters (and possibly of the splenic veins) by action of venomotor fibers

Reservoir Function

In addition to hemorrhage and hypoxia, this function is brought about by exercise, psychic influences, raised external temperature, certain types of anesthesia (chloroform), certain humoral agents and drugs, and, subacutely, in estrus, pregnancy, and lactation Under pentobarbital anesthesia, which apparently promotes maximal storage, *severe hypoxia* caused the spleen of the dog to discharge 16 to 20 per cent of the normal circulating blood volume (Kramer et al.) This is in line with older estimates of splenic discharge in dogs in response to exercise and hemorrhage (Barcroft and Stephens, 1927) This discharge produced an increase of 10 5 per cent in the systemic hemoglobin leading to the estimate that blood stored in the spleen must carry approximately 40 Gm per cent of hemoglobin, which corresponds to 95 per cent cell volume in the splenic stores Although this may seem unduly high, in lightly morphinized dogs the splenic hematocrit was found to be 80 per cent, compared to the systemic average of 43 per cent

The oxygen capacity of the splenic vein blood was found to be 80 per cent higher than arterial blood During hypoxia, this may be considered as a small emergency store of oxygen, for about 30 to 60 ml oxygen are released with the 100 to 200 ml of stored splenic blood The volume of blood per gram of tissue is indeed high in the spleen compared to other organs, in dogs, 0 420 per gram as compared to 0 200 in the liver and 0.060 in the bowel; in the rat, 0 481 in the spleen as compared to 0 178 in the liver.

Splenic Blood Flow

Grindlay et al (1939) studied splenic inflow and outflow in intact dogs using thermostromuhrs. At rest and during sleep, flow averaged 97/ml/min in the splenic artery. During feeding, flow in both vein and artery increased by 26 to 100 per cent and lasted for 3 to 5 hr. During exercise on a treadmill, an increase in both arterial and venous flow was noted, but not immediately in the artery, signifying initial emptying of the spleen. Shivering brought on by sojourn in a cold room also increased splenic flow, probably as a result of increased skeletal muscle activity. Sudden noise caused splenic discharge, as evidenced by a 38 to 154 per cent increase in venous flow for a minute, with no change in arterial flow. With hemorrhage, arterial flow fell sharply, while venous flow showed an initial transitory increase, again signifying discharge. Ether anesthesia had no effect, but pentobarbital caused flow to increase by an average of 32 6 per cent. Epinephrine and ephedrine caused a temporary decrease in flow, preceded by a transitory rise. Pitressin and acetylcholine decreased flow. Histamine caused arterial flow to decrease, but venous flow increased at first (discharge), then decreased.

Splenic Rhythm. A rhythmic change in splenic volume was observed to occur in cats at the rate of 25 to 50 sec This could be initiated by sudden elevation of blood pressure, restoration of respiration after stoppage, temporary interruption of the splenic circulation, or histamine injection, followed by decrease in blood pressure The rhythm could be induced both in excised and perfused spleens. Small undulations in systemic arterial pressure accompanied this rhythmic change in volume, a small rise associated with discharge, and return with restoration of volume Except that it is associated with instability of the circulatory homeostatic mechanism, the significance of splenic rhythm is not known.

LIVER

Anatomy

Elias (Part 1, Chap 11) has suggested the substitution of the concept of hepatic lamina for the

or stoppage of flow occurred first in venules (at 15 mm Hg pressure), then in small veins (20 mm Hg), then in venous capillaries (30 mm Hg), followed in order by arterioles, small arteries, then arterial capillaries. Flow stopped at 50 to 70 mm Hg, except for slight flow in mural veins and arteries. Distending pressures of 30 to 40 mm Hg created disturbances which were completely reversible, but pressures of 50 mm or above produced irreversible changes in the mural circulation and intestinal wall, with permanent interruption of flow of many small vessels, interstitial hemorrhage, and pronounced intravascular agglutination of cells. With blockage of veins as the first event, increased capillary pressure causes leakage of plasma into the wall of the gut and into the lumen If excessive, this will lead to shock, as often occurs with intestinal obstruction. The seriously impaired arterial circulation at the higher distending pressures promotes breakdown of the wall of the gut, furthered by proteolytic digestion of tissue, and leads ultimately to gangrene and rupture. Distention of the dog intestine to 30 cm water has been shown to reduce intestinal oxygen consumption, probably basic to these changes (Lawson et al.).

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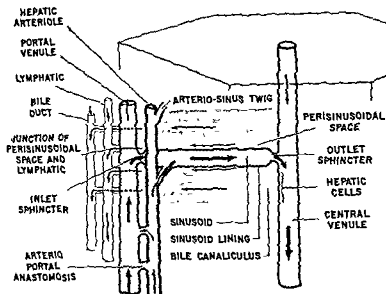
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This is achieved by sympathetic outflow in splanchnic nerve branches accompanying the artery into the spleen, presumably mediated by



CC/MIN/GM

h = 0.45 ☐
h < 0.0025 { ● P_{O_2} = 1 ATM; ○ P_{O_2} = 3 ATM }

$b/b_{13.5}$

P_b (CM PLASMA)

B

Fig 2.75 A. Diagram of the liver lobule The arrows indicate the *direction of flow*. For clarity of presentation *neither the nerves* nor lymphatic vessels which surround the central venule are shown A network of *nerves surrounds all* tubular structures (From Bloch, 1955.) B. Pressure-flow relations for the isolated *rat liver preparation perfused* with rat plasma (hematocrit < 0 0025) or with whole rat blood (*hematocrit* 0.45) *Flow is* given both in absolute values (cc/min/gm), and as a ratio of experimental flow to the flow observed at a standard perfusion pressure of 13 5 cm plasma ($b/b_{13.5}$). (*From Brauer et al*, 1956)

conventional idea of the cord structure (two cords of hepatic cells with an enclosed sinusoid on one side and a bile capillary on the other). The hepatic lamina consist of the thickness of one cell and are perforated at frequent intervals to permit passage of the sinusoids The concept of the hepatic circulation summarized here is based on this anatomic conception.

Hepatic Artery. This is not an end artery, but it has many collateral connections. It supplies Glisson's capsule and investing connective tissue, the bile ducts, and interlobular septa. Anastomotic connections with the portal vein occur at several levels in the interlobular spaces, or to terminal branches of the portal vein just before these enter the sinusoids (Fig. 2-75A). Terminally, intralobular hepatic arterioles and arterial capillaries empty into the sinusoids, supplying both the interior *sinusoids in the central part of* the lobule, as well as peripheral sinusoids Ligation of the hepatic artery may or may not be compatible with survival, depending upon the level of ligation and the species. In the dog, if ligation is at the point of entry to the liver, death ensues The rat, however, may survive such ligation because of more numerous collaterals If ligation in the dog is done beginning distad to the liver (common hepatic artery), survival depends on the opportunity for development of collaterals from small arteries in the diaphragmatic ligaments, along the common bile duct, and from the small arteries supplying the vena cava below the diaphragm

Portal Vein. This supply comes from the intestinal tract, pancreas, and spleen India ink injection studies have shown that streamlined flow occurs, so that the splenic vein empties into the left lobe and the superior mesenteric vein into the right lobe. Thus the upper gastrointestinal tract, parts of the colon, and spleen go to the left liver, and the remainder of the flow goes to the right Although functioning primarily to carry digested foodstuffs from the intestine to the liver, the portal vein serves also to support the liver integrity. When an *Eck fistula* is created, hepatic atrophy and deranged hepatic structure and function develop. The liver is reduced to about one-half normal size, the tissue becomes flabby, pale, and mottled yellow. Central portions of the lobule atrophy and become filled with fat.

Sinusoids. Conducting portal vein branches give rise to small distributing veins These, as well as smaller axial portal vein branches, give off inlet venules which enter the lobules through holes in the limiting lamina. Beyond this, *the inlet venules* branch into sinusoidal arborizations. The terminal end of the portal vein branches split directly into sinusoids, *the "exchange"* vessels of the liver

The sinusoids are smooth-walled, branching, anastomosing cylindrical tubes. They are believed to be lined with phagocytic Kupffer cells, but none were found projecting into the lumen of the sinusoids. The sinusoids are slightly ampullated in shape just before they join the draining veins, giving the impression of a sphincter. Also, they appear narrowed at the point of inlet from the venules.

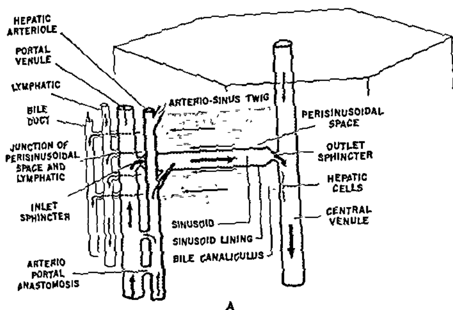
Veins. The sinusoids empty into the central vein of the lobule which connects to the sublobular veins These in turn converge into the hepatic veins, which discharge into the inferior vena cava *Strong muscular sphincters* have been found in the hepatic vein of dogs, but *not* in the human being. These sphincters may aid in regulating hepatic venous outflow.

Intermittence of Flow

The presumption that sphincters are located at the entry and exit of the sinusoids, permitting regulation of flow and storage of blood, has given rise to the concept of intermittence of flow. Such has been observed in the frog and in the rat. It has been suggested that the number of sinusoids which are open varies greatly in the frog, with frequent shifts of activity. In the rat, however, more than 75 per cent of the regions studied displayed inactivity when neither excitatory nor inhibitory factors were operative in the intact liver. The reasonably steady hepatic blood flows which have been observed in the dog and man confirm this trend toward a basal state of inactivity.

Nervous Regulation

Because of the complexity of the vascular bed of the liver, an analysis of nervous regulation is difficult. By direct observation of liver flow, sympathetic stimulation has been seen to cause constriction of arterioles, sinusoids, and, indeed, all intrahepatic vessels. It must be kept in mind that some of these changes, e.g., sinusoidal constriction, may *be due to a* "passive recoil" effect as the result of arteriolar constriction It appears from studies with x-ray opacity techniques, that the constrictor influence *upon* smaller vessels varies in different regions of the liver Little is known about the control of the arteriovenous shunts which exist in the liver Dilatation of the liver vessels apparently cannot be induced by vagal stimulation It is therefore doubtful that specific vasodilator fibers run to the liver. Finally, it should be kept in mind that the extrinsic control of the liver circulation adds further complexity, since vasomotor changes in



CC/MIN/GM

$h = 0.45$ □ } P_{O_2} = 1 ATM
$h < 0.0025$ { ● P_{O_2} = 1 ATM; ○ P_{O_2} = 3 ATM

$b/b_{13.5}$: 0, 0.5, 1.0, 1.5
CC/MIN/GM: 0, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0

P_b (CM PLASMA): 0, 5, 10, 15

B

Fig. 2-75. A Diagram of the liver lobule. The arrows indicate the direction of flow. For clarity of presentation neither the nerves nor lymphatic vessels which surround the central venule are shown. A network of nerves surrounds all tubular structures. (From Bloch, 1955.) B Pressure-flow relations for the isolated rat liver preparation perfused with rat plasma (hematocrit < 0.0025) or with whole rat blood (hematocrit = 0.45). Flow is given both in absolute values (cc/min/gm), and as a ratio of experimental flow to the flow observed at a standard perfusion pressure of 13.5 cm plasma ($b/b_{13.5}$). (From Brauer et al., 1956.)

TABLE 2-6 SUMMARY OF DIRECT HEPATIC BLOOD-FLOW STUDIES IN DOGS IN WHICH SEPARATE HEPATIC ARTERY AND PORTAL VEIN MEASUREMENTS WERE MADE

Worker	*Method*	*Anesthetized*	*Portal flow, ml/min*	*Hepatic arterial flow, ml/min*	*Hepatic arterial flow, % of total*	*Total flow, ml/min*	*Ml/kg/min*	*Ml/100 Gm/min*
Burton-Opitz (1911)	Direct stromuhr	Y	268	144	35	412	39 5	84
Macleod and Pearce (1914)	Total outflow	Y	270	120	30	390	44 0	95
Grab, Janssen, and Rein (1929)	Thermostromuhr	N	268	62	19	330	26 0	58 5
Blalock and Mason (1936)	Total outflow	N	374	83	18	457	28 6	86 0
Grodins, Osborne, Ivy, and Goldman (1941)	Thermostromuhr	Y	147	144	49	291	23 0	
Grindlay, Herrick, and Mann (1941)	Thermostromuhr	Y	383	75	16	458	22.6	86 0 *
Selkurt and Brecher (1956)	Bristle flowmeter	Y	309	175	36	484	22 2	85 6
Average			288	115	29	403	29 4	82 5

* Estimated

TABLE 2-7 SUMMARY OF HEPATIC BLOOD-FLOW STUDIES DONE WITH INDIRECT (DYE-REMOVAL) METHODS

Worker	*Method*	*Anesthetized*	*Total flow, ml/min*	*Ml/kg/min*	*Ml/100 Gm/min*
Lipscomb and Crandall (1947)	Urea excretion	N	383	32 0	
Werner and Horvath (1952)	BSP	Y	690	42 0	140
Pratt, Burdick, and Holmes (1952)	BSP	N	749	48 6	
Heinemann, Smythe, and Marks (1953)	BSP	Y	437	27 6	
Smythe, Heinemann, and Bradley (1953)	BSP	Y	540	29 5	
Selkurt (1953)	BSP	Y	677	35 4	130
Casselman and Rappaport (1954)	BSP	Y	507	37 0	156
Sapirstein and Simpson (1955)	Rose bengal	Y	577	31 5	
Average			570	35 5	

the intestine and spleen will modify portal vein inflow, aside from any direct neurogenic or humoral influences on the liver

The Measurement of Hepatic Blood Flow

Numerous techiniques, direct and indirect, have been used for the measurement of liver blood flow (Tables 2-6 and 2-7). The indirect methods are based on the Fick principle, the most widely used being the BSP (Bromsulphalein) method devised by Bradley et al (1945)[1] Consideration of the direct flow data in Table 2-6 reveals that about

[1] Principle (as employed in man) Infuse 3 mg/min/m² surface area, after 150-mg priming dose E H B F (effective hepatic blood flow) =

$$\frac{R}{0.01(P-H)} \times \frac{1}{1-\text{hematocrit}}$$

where R is rate of dye removal (mg/min); P is peripheral venous dye concentration in mg per 100 ml, H is hepatic venous dye concentration in mg

one-fourth the total hepatic flow is delivered by the hepatic artery in dogs It will be noted that on a per kilogram basis, the indirect measurements yield the higher total flow figures. Granting that operative procedures may have fostered the lower direct flows, yet another argument has been evoked to explain the higher dye-method figures, and this is that extrahepatic dye removal may account for the somewhat higher apparent blood flows This argument is based on comparison of dye removal (BSP) in intact as compared with hepatectomized dogs (Horvath et al) But the protagonists of the method insist that the rate of removal of the dye by extrahepatic tissue is negligible compared with hepatic removal (Casselman et al, Selkurt, 1953, Bradley, 1950). Enterohepatic recirculation of the dye does not seem to be an important source of error Evidence has been presented that sampling from different hepatic veins does not influence the BSP extraction figures (about 34 to 40 per cent), so long as the catheter does not reflux inferior vena cava blood

The BSP method has been applied to man by a number of investigators, and the results are consistent at a figure of about 1,470 ml/min (850 ml/m^2/min) Myers (1947) compared the BSP method with the urea-excretion method and found 800 and 1,000 ml/m^2/min, respectively The liver flow has been compared in several mammalian species using the chromic-PO_4 disappearance technique The following figures are given in volumes of blood [illegible]

[illegible] 1 40 ± 0 1, mouse (anesthetized) 1 70 ± 0 1, rat (normal) 1 20 ± 0 1.

HEMODYNAMIC CONSIDERATIONS

Although about one-fourth of the liver blood supply is delivered by the hepatic artery at approximately the pressure gradient existing in the systemic arterial system, the greater bulk enters the sinusoids at portal venous pressure, about 8 mm Hg in the dog (Selkurt and Brecher, 1956). In this series, hepatic venous pressure averaged 2 mm Hg, so that the perfusion pressure gradient was 6 mm Hg. This gradient was estimated at about 10 mm Hg in man (13 mm Hg in the portal vein to 3 mm Hg in the hepatic vein) Brauer et al (1956) have made an extensive study of the hemodynamics of portal vein flow in the isolated rat liver. They obtained a mean flow of 2.79 ± 0 28 ml/Gm/min at a mean perfusion pressure of 13 5 cm When oxygenated plasma was used for perfusion, the figure increased to 4 99 ± 0.17, illustrating the effect of lowered viscosity on flow The pressure-flow curves appeared to be sigmoid in shape (Fig 2-75B). Flow began at about 4 cm for blood (critical closing pressure?) and increased more rapidly at first than pressure (i e , convex to the pressure axis) Above 13 cm, flow was approximately proportional to pressure, increasing to 3 6 ml/Gm/min at about 17 cm The plasma curve began at 2 cm and reached about 6 5 ml/Gm/min at 18 cm, and was more sigmoid in character. The increased flow as pressure was elevated was concluded to be the result of increase in mean effective vessel radius in the approximate range of 4 to 12 cm perfusion pressure From these considerations it is apparent that the level of perfusion pressure in the portal vein is an important determinant of total liver flow. Thus, any modification of vasomotor tone (neurogenic or humoral) in the intestinal vascular bed could significantly influence liver flow, as would also splenic discharge Finally, since the portal-hepatic vein gradient is a small one, it is conceivable that changes in inferior vena cava pressure could significantly alter flow

Splanchnic Oxygen Utilization

The studies of Blalock and Mason revealed that hepatic oxygen utilization in unanesthetized dogs averaged 23 8 ml/min (range, 13 2 to 32 6), or an average of 0 045 ml/Gm/min (0 025 to 0 065) Oxygen contents were hepatic artery, average 16 13 vol per cent, portal vein, average 10 51, and hepatic vein, average 6 42 Mesenteric utilization (intestine, spleen, pancreas) can be calculated to be 20 4 ml/min, or a total splanchnic utilization of 44 2 ml/min

per 100 ml, R is determined by adjusting rate of infusion, I, of dye so that blood levels do not change

Validity of the method depends on the following conditions (1) BSP must remain in the plasma and be removed exclusively by the liver, (2) concentration of dye in the peripheral venous blood, P, must be the same as that in blood supplying the liver (i e, hepatic artery and portal vein), (3) with catheter technique, concentration in any one hepatic vein should be representative of *total* hepatic venous outflow

If plasma level is changing, a correction can be made by measuring or estimating plasma volume, P.V. If rising $R = I - (\Delta P \times P.V.)$ If falling $R = I + (\Delta P \times P.V.)$

This has been confirmed at 38 ml/min and 43.15, or approximately 2.0 ml/kg/min In man, splanchnic oxygen consumption has been calculated in separate studies to be 41 and 34 ml/min/m². From these data, oxygen utilization by the liver of man has been computed to be 0.05 ml/Gm/min, a figure close to that of the dog liver. The hepatic artery supplies about 35 per cent of the liver oxygen supply, but this can vary up to 70 per cent (Selkurt et al., 1956). Following hemorrhage, increased arteriovenous oxygen difference across the splanchnic bed provides a reasonably constant supply of oxygen despite reduction in blood flow. With severe and prolonged hypotension, oxygen utilization of both the liver and intestine is depressed. Under these circumstances, *there is a trend for greater contribution from* the hepatic artery, as portal oxygen tension drops to low levels.

Factors Which Modify Hepatic Blood Flow

Hemorrhage curtails hepatic blood flow in proportion to the degree of depletion of the blood volume. One of the surprising observations noted in most of this work, however, is that *total splanchnic vascular resistance* does not increase to any marked degree, and that flow decreases in approximate proportion to blood pressure decrement. Indeed, it has been observed that after hemorrhage, hepatic blood flow actually makes a certain degree of recovery within 23 to 70 min after sustained blood loss. No explanation for this behavior of the splanchnic bed is forthcoming, although one may speculate that hypoxic states may promote the accumulation of metabolites or humoral substances that favor splanchnic hyperemia. Figure 2-76 illustrates response of the splanchnic bed of dogs to prolonged hemorrhagic hypotension. With restoration of blood pressure *after transfusion*, a *marked* overshooting of the portal flow is observed during the early phases of normovolemic shock, the result of "opening up" of the intestinal bed during hypotension.

Epinephrine and Norepinephrine. Direct injections into the liver circulation or local ap-

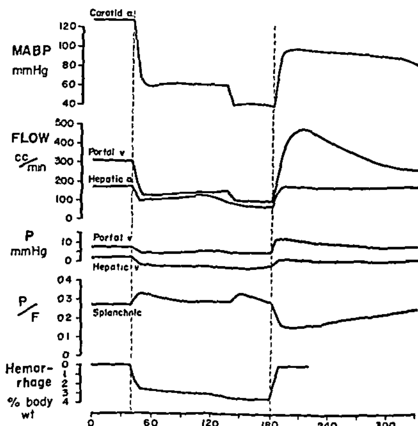


Fig. 2-76. Mean trends in splanchnic hemodynamics during standardized shock procedure in dogs Flow was measured with bristle flowmeters A, Oligemic shock; B, normovolemic shock; P, venous pressure, P/F, ratio of arterial-hepatic venous pressure over total splanchnic flow (portal plus hepatic artery) (splanchnic vascular resistance). (From Selkurt and Brecher, 1956.)

plication of *epinephrine* induce a prompt vasoconstrictor response. When low epinephrine concentrations are given, mostly vasodilator effects occur, with evidence of concomitant "metabolic" effects on the liver. Either epinephrine in small concentration has a direct dilating effect on the vascular elements, or some secondary metabolic by-product may be responsible for the dilating effect. Norepinephrine, whose "metabolic" influences on the liver are weak, causes a constrictor action exclusively.

Other Factors. Histamine causes an increase in hepatic blood flow in man, concomitant with a decrease in blood pressure, suggesting that it may effect active dilatation of the splanchnic bed

Ethyl alcohol in narcotizing doses given by gavage tube to dogs was found to have no significant effect on hepatic blood flow. Pyrogenic substances have a marked hyperemic action on the splanchnic circulation

Abdominal compression, creating an increase of about 20 mm Hg in intraabdominal pressure, results in reduction of hepatic blood flow, probably by raising portal pressure and restricting sinusoidal perfusion

During the phase of developing *syncope* induced by occlusion cuffs to the thighs, splanchnic blood flow is diminished, with increase in calculated vascular resistance. At the time of fainting, hepatic blood flow decreases as blood pressure falls, but the calculated vascular resistance actually diminishes, an apparent "opening up" of the splanchnic bed at the time of the faint.

Muscular exercise reduces splanchnic blood flow, thus shunting more to the muscles and brain

Clinical Conditions. Certain clinical conditions result in alteration of hepatic blood flow. It is significantly reduced in *congestive heart failure*, to 535 ml/min/m^2, compared with the control series of 850 Oxygen utilization is not changed, since the arteriovenous difference increases as blood flow is reduced, 8 4 as compared to 4.5 vol per cent in normal persons. Hepatic blood flow is often decreased in *cirrhosis of the liver* Bradley et al. (1948) found it below normal in 7 of 17 subjects, regardless of etiology of the cirrhosis. These ranged from a total of 492 to 990 ml/min Seven others fell in the normal range, and, surprisingly, 3 were found to have elevated flows (2,325 to 4,620 ml/min). The latter were accompanied by very low BSP extraction figures (3 4 to 8.4 per cent), compared to the expected normal in human beings of about 50 per cent. Usually, oxygen arteriovenous differences were increased A slight increase in flow was noted in *hyperthyroid* patients, 880 ml/min/m^2, as compared with the control series of 810, but flow was reduced as per cent of cardiac output (17 as compared to 19) Arteriovenous oxygen difference increased to 6 3 vol per cent from 4 3, and splanchnic oxygen consumption was elevated to 54 ml/min/m^2, as compared to the control of 34.

Coronary circulation

DONALD E. GREGG

GENERAL CONSIDERATION

Following are some general comments on the coronary circulation and ways of studying it in dog and man

The Coronary System In man, approximately 50 per cent of hearts have the right coronary artery predominant, 30 per cent have a balanced coronary circulation, and 20 per cent have the left coronary artery predominant The arterial pattern of the dog heart compares with the situation in man in which the left coronary artery is predominant. In the latter, the left coronary artery nourishes about 85 per cent of the heart muscle, supplying the whole of the left heart as well as portions of the right ventricle (Schlesinger).

Each of the two coronary arteries connects with its capillary and superficial venous bed and with the right atrium. The epicardial branches of the coronary arteries and veins also anastomose with each other and with extracardiac arteries and veins There are also numerous arteriovenous shunts In addition, the arterioles, together with the capillaries and superficial veins, connect directly with both ventricular cavities by discrete channels which together comprise the deep coronary drainage circuits (Gregg, 1950).

Preparation and Methodology. Only results from the human being and anesthetized dog are considered The objective of studies of the coronary circulation is knowledge of the determinants of coronary flow, of the oxygen uptake (coronary flow × coronary arteriovenous oxygen difference) by the myocardium, and of their relation to the work of the heart in states of normalcy, of increased or decreased stress, and of disease in man This objective is far from being realized.

The Pitot tube, orifice meter, rotameter, bubble flowmeter, and thermostromuhr are used to measure coronary flow by insertion between the cut ends of a coronary vessel. The thermostromuhr also measures flow in the intact coronary artery. In addition, the nitrous oxide method can be used in the normal dog and human being, and if used with care, reasonably accurate values for human beings can be obtained. All except the bubble flowmeter and nitrous oxide methods permit continuous recording of flow All measure mean flow, the orifice meter can be used for recording phasic flow (Potter, Gregg and Green, 1940b).

The oxygen saturation of coronary arterial and venous blood is obtained by continuous withdrawal of aliquots of the respective bloods through indwelling tubes and their analyses by the Van Slyke, Beckman, or oximeter techniques. The first two methods give average oxygen values over a period of time, the last permits continuous recording of the arteriovenous oxygen difference (Gordy et al, Kramer et al, Wood, Sabiston et al, 1957a).

Utilization of the Superficial Versus the Deep Drainage Circuits in the Normal Heart. All blood in the superficial veins of the heart arises in the two coronary arteries and none comes from the deep-lying connections within the cardiac cavities In flow balance studies, essentially all blood entering the right and left coronary arteries can be collected in the superficial veins of the heart, most of the right draining by the anterior cardiac veins, most of the left by the coronary sinus, and with considerable overlap in the use of the two venous drainage systems by the two coronary arteries This leaves little blood to drain by way of the deep channels into the cardiac cavities (Gregg and Shipley, 1947). Presumably a similar utilization of anatomic pathways exists in man However, in man, it is reported that 16 per cent of left coronary flow enters the left ven-

icular cavity by the deep drainage channel (Bartels et al.).

The deep drainage channels could have an important functional role if they served as arterial channels from the left ventricle to the myocardium during coronary artery constriction or occlusion, or as venous channels for the whole myocardium in the presence of extensive superficial vein constriction or occlusion. Regarding the first situation, although essentially complete occlusion of the coronary arteries in human beings has been found at autopsy, the presence or extent of development of extracardiac arterial collaterals is not known. In addition, with functional separation of one or both coronary arteries from the aorta, no blood flow from the ventricles into the superficial coronary venous system can be demonstrated and the hearts do not survive. Regarding the second situation with acute closure of all visible superficial coronary veins, although such hearts may survive, large intra- and extracardiac superficial venous channels quickly appear. Hence, known observations are conflicting and any conclusion is difficult regarding the utilization of deep coronary venous drainage channels in diseased hearts (Gregg and Shipley, 1947).

Use of Left Coronary Artery Flow Together with the Chemical Composition of Coronary Sinus Blood as an Index of Left Ventricular Metabolism. It is not possible to quantitate accurately the metabolism of the right ventricle because its superficial anterior cardiac veins have many exits into the right atrium and their contained blood is grossly contaminated by blood from the left coronary artery. However, drainage of the left myocardium is accessible. In most instances quantitative changes in the metabolism of the left ventricle can be obtained from measurement of the chemical composition of the coronary sinus blood together with the left coronary inflow, because (1) coronary sinus blood is almost entirely from the left coronary artery, (2) coronary sinus flow constitutes from 70 per cent to as much as 95 per cent of left coronary inflow, and (3) the oxygen content of the venous blood from the left coronary artery not draining into the coronary sinus is generally only slightly less than that in the coronary sinus (Rayford et al.). This is a very important and practical consideration because of the widespread use of these measurements for just this purpose.

BASIC REGULATION OF CORONARY FLOW AND MYOCARDIAL METABOLISM

Basal Data (for selection, see Fig. 2-77). In the resting state, the coronary data for dog and man agree. With the left ventricular cardiac work index approximating 3.5 to 4.6 kg, left coronary flow approximates 72 to 85 ml/100 Gm left ventricle per minute. Although the heart can remove essentially all oxygen from the coronary blood in its passage through the myocardium, normally about two-thirds is extracted with an arteriovenous difference of 12 to 14 ml and a coronary sinus value of 4 to 5 ml. This extraction changes little with increased stress, signifying that the oxygen supply is well balanced with metabolic demands (Rowe et al., 1956, Gregg and Shipley, 1944, Foltz et al.).

Oxygen uptake per 100 Gm left ventricle is 8 to 10 ml/min, of which a considerable portion occurs during diastole or the resting state. The resting metabolism (absence of heart rate, cardiac output, and arterial blood pressure) during cardiac arrest by vagal stimulation or potassium injection in hearts with perfused coronary arteries approximates 2.5 ml/100 Gm left ventricle per minute, or about 25 to 30 per cent of that at the prior working level. The metabolism of the nonworking (but slowly beating) heart, obtained by rapid exsanguination is about the same, while that of the fibrillating heart is considerably greater. Oxygen consumption during systole averages about three times that in diastole for the same period (McKeever et al., Paul et al., 1954).

The metabolism of the heart is predominantly aerobic. However, with abrupt vagal stoppage, an excess of oxygen (*oxygen debt*) over that in the resting state is taken up by the heart from the onset of asystole to the time of appearance of the resting metabolism. This amount of oxygen, which is small (8 per cent compared to the near maximum oxygen debt for an equivalent weight of skeletal muscle of man), could well be greater in a heart working near capacity (McKeever et al.)

As in any muscle, the mechanical efficiency of the left ventricle is estimated by dividing its external work by the difference between its oxygen consumption during activity and during its resting state. Published data which indicate a normal efficiency approximating 20 per cent include only the first two measurements (Bing

	SYSTEMIC							CORONARY							
	ART B. P.	CI	CWI	SVI	SWI	HR		L.C.F. CC/MIN / 100 GM	$\frac{P}{C.F.}$	C.S. O_2 CC	COR A-V O_2	O_2 CC/MIN / 100 GM	SCF *	SCO_2 ■	$\frac{CW}{O_2}$
HEART RATE #	↗	↗	↗	↘	↘	↗		↗	↘	→	→	↗	↘	↘	↘
TRANSFUSION #	↗	↗	↗	↗	↗	↘		↗	↘	→	→	↗	↗	↗	↗
SYMPATHETIC NERVES #	↗	↗	↗	↘	↘	↗		↗	↘	↘	↗	↗	↘	↘	↘
ANEMIA #• MODERATE	→	→	→	→	→	→		↗	↘	↘	↘	→	↗	→	→ #
ANEMIA #• SEVERE	↗	↗	↗			↗		↗	↘	↘	↘	↗			→ #
THYROID #•	→	↗	↗	↗	↗	↗		↗	↘	→	→	↗	↗	↗	
EPINEPHRINE, NOREPINEPHRINE #	↗	↗	↗	↘	↘	↗		↗	↘	↘	↗	↗	↘	↘	↘
AORTIC COARCT. #• MODERATE	↗	→	↗	↗	↗	↘		↗	↘	→	→	↗	↗	↗	↗ #
AORTIC COARCT. #• COMPLETE	↗	↘	↘	↘	↘	↘		↗	↘	→	→	↗	↗	↗	↘ #
AORTIC STENOSIS #	↘	↘	↘	↘	↘	→		↗	↘	↘	↗	↗	↗	↗	↘ #
PULM. STENOSIS # ▲	↘	↘	↘	↘	↘	→		↗	↘	↘	↗	↗	↗	↗	↘ #
H C.V D •	↗	→	↗	→	↗	→		→	↗	→	→	→	→	→	
HEART FAILURE #•	↘	↘	↘	↘	↘	→		X	↘	↘	↗	X	X	X	↘
SHOCK #•	↘	↘	↘	↘	↘	↗		↘	↘	→	→	↘	↘	↘	↘ #
HYPOTHERMIA #	↘	↘	↘		↘	↘		↘	→	→	→	↘	↘	↘	→

= DOG • = HUMAN ▲ INDICATED DIRECTIONAL CHANGES REFER TO RIGHT VENTRICLE * STROKE COR. F. ■ STROKE COR. O_2

(Legend on facing page.)

et al, 1949). Since the resting metabolism is considerable and values are generally not available, only the relation of cardiac work to total oxygen uptake will be considered.

Physical Control. Coronary flow is related to the pressure difference (effective pressure) between the central coronary artery (identical to aortic pressure) and the right atrium divided by the sum of the viscous resistances to flow in the epicardial portion of the artery and in the peripheral coronary bed Viscous resistance to flow (aside from change in hematocrit) is mainly governed by the mean caliber of the coronary vascular bed. Since the arterial resistance is negligible, the mean coronary diameter and hence flow are controlled by the *effective intravessel pressure* and by two peripheral mechanisms, active changes in the *state of the small mass of intravascular smooth muscle built into the* coronary vessels, and the *mechanical or passive effect on flow* exerted during ventricular systole by the large extravascular muscle *mass around the* coronary vessels.

Insight into the complexity of the integrating action of these three flow determinants has been obtained from recording of the peripheral coronary pressure and the phasic, or moment-to-moment changes, in coronary inflow and outflow in the epicardial arteries and veins (Fig 2-78). At the onset of isometric contraction of the left ventricle, there is an abrupt decrease in left coronary inflow (solid line) or even the appearance of backflow With the rise in aortic pressure, forward flow increases initially and rapidly, only to decrease to a new intermediate level in late systole With the onset of isometric relaxation, coronary flow increases significantly, peaking at early diastole and then declining progressively. The velocity of coronary inflow differs somewhat from the estimated intramyocardial flow (dotted line). The deficit during isometric contraction is caused by the compressing action of the myocardium on the coronary capillaries, forcing blood into the superficial vessels. Early in the period of ejection, the flow excess is caused by the uptake of blood in the superficial coronary arteries, in diastole, the excess is caused by the uptake of blood to fill the previously compressed capillaries. These demarcations of flow are much less obvious in the right coronary inflow pattern, which roughly resembles the prevailing aortic pressure curve Thus, blood is flowing *through the* myocardium throughout the cardiac cycle, except possibly for a brief period in early *systole* in the left coronary artery. In the left coronary artery, the systolic rate of flow is *less than that during diastole*, in the right coronary artery, the systolic rate equals or exceeds the diastolic. *In contrast to the left* coronary inflow pattern, *the flow curves in the coronary* sinus and anterior cardiac veins rise and fall smoothly, with most flow occurring during systole and very little during diastole (Gregg, 1950; Gregg and Green, 1940, Johnson et al)

The preceding account indicates that the coronary bed has a fluctuating resistance *to*

Fig. 2-77. Response of the coronary circulation to primary stress states Certain criteria were used in selection of data A number *of observations* for any one variable was *necessary* All comparisons of coronary flow to oxygen usage per 100 Gm *left ventricle* per minute had to approximate the *same line* representing a given coronary *arteriovenous* oxygen difference, this relationship of flow to oxygen having been previously *established* by a large number of *careful experiments* in dogs. Selection of basal *data* in the dog and man was *restricted to* those in which *arterial blood* pressure, *cardiac* index, cardiac *work index, and heart* rate or body oxygen uptake *roughly approximated* those figures *acceptable for the* resting state. In the abnormal *or diseased* state in human beings, data were restricted to those in which the *systemic* blood pressure, cardiac index, cardiac work index, and heart rate approximated those *regarded as acceptable* for the basal state when there was no known reason [illegible] work on human [illegible] valvular lesion [illegible] the dog data [illegible] *more* reliable However, the fact that when left *coronary flow is* compared to the oxygen usage per 100 Gm *left ventricle* per minute most *data* using the nitrous oxide method *in* human beings falls on the same coronary arteriovenous *difference* line as in the dog, lends considerable support to the accuracy of this method *when properly used. Despite* these precautions the data are doubtless *subject to considerable* error because *of the* crudity of methods in human beings and the lack *of a normal* environment in dogs.

coronary flow. In the left coronary artery, the peripheral coronary maximal systolic and minimal diastolic pressure values approximate 80/20 mm Hg, respectively, and inflow is cut off at these pressure levels when the left coronary artery is perfused under constant pressure (Fig 2-78). In the right coronary artery, the contour and time relations of the peripheral coronary pressure curve are similar, but the values for systole and diastole and for the cutoff of flow are considerably lower (Gregg, 1937; Green et al., 1935).

Elevation of right atrial pressure must increase coronary venous pressure and decrease the flow of blood in the coronary arteries provided no compensatory mechanisms set in Such studies have not been made. However, mild elevation of the pressure in the coronary veins, draining the left coronary artery by coronary sinus constriction, may only decrease coronary flow and increase coronary arteriovenous oxygen difference. Even marked constriction of, or clamping of, the coronary sinus may cause only moderate reduction in arterial pressure and left coronary flow. The smallness of the effect on coronary flow, despite elevation at times of the coronary venous pressure to near aortic systolic level, is presumably caused by the compensatory increased functioning of collateral venous communications with the anterior cardiac veins, whose flow increases considerably. Similarly, right coronary inflow is not greatly reduced by clamping most of the anterior cardiac veins, presumably for the same reason (Gregg and Dewald, 1938b).

The relation of coronary perfusion pressure to coronary flow (*P/CF*) is generally such that the calculated coronary resistance decreases as

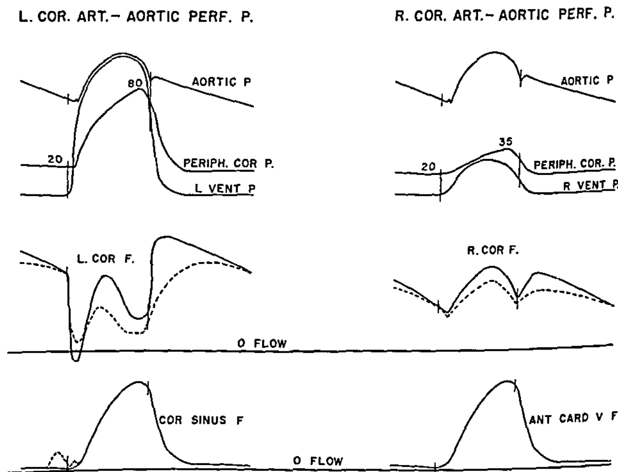


Fig. 2-78. Series of curves relating variations in left and right coronary inflow, coronary sinus, and anterior cardiac vein flow to aortic pressure, ventricular pressure, and peripheral coronary pressure. Coronary inflow (solid lines) obtained with orifice meter, anterior cardiac vein flow also with orifice meter, coronary sinus flow with Pitot tube Broken lines, estimated intramural velocity curves For details see text.

the coronary flow rises. This holds for almost any dynamic state of the coronary system (excised fibrillating or beating heart, heart in situ) and also exists in the pulmonary artery, peripheral vascular beds, and in an artificial set of rigid tubes (Osher). In the heart, it is impossible to say what fraction of the flow change is caused by passive dilatation from the perfusion pressure per se, since the oxygen consumption per minute and per heart beat is elevated without any other observable systemic dynamic change (Gregg, 1957). Accordingly, if a physiologic variable alters coronary pressure and flow by about the same amount and hence the ratio is unaltered, it is impossible to know whether the change in coronary flow is due to a change in effective head of pressure alone or whether the variable directly affected resistance. However, a gross change in the vasomotor state of the bed occurs when coronary flow changes considerably with a constant pressure, or flow and pressure change considerably in opposite directions.

Extravascular compression is controlled by changing tension in the myocardial wall. It is obviously related to the duration and height of pressure with each systole and the number of ventricular contractions per minute. Reduction in systolic duration will increase coronary flow, while shortening of diastole will reduce coronary flow per beat. Ventricular contraction acts to impede coronary flow, as demonstrated by the immediate elevation of coronary inflow and outflow in vagal stopped hearts with perfused coronary arteries. Normally ventricular systole limits coronary flow by 30 to 80 per cent, the effect varying greatly under different conditions. With electrically induced ventricular fibrillation, coronary inflow and outflow also rise greatly (Sabiston and Gregg, 1957; Gregg, 1955).

Chemical Control. The coronary flow is greatly increased and the coronary arteriovenous oxygen difference decreased by some chemical constituents of the blood, but this response does not occur with others; in both cases there is little or no change in systemic dynamics (blood pressure, cardiac work, heart rate) or myocardial oxygen consumption. The coronary response to carbon dioxide and decreased pH is minimal (Eckenhoff et al., 1947), intracoronary injection of intermediate metabolites will increase coronary flow and decrease oxygen extraction (Wolf et al.), but it is doubtful that the normal concentration of these chemicals within the coronary vessels effectively alters flow, since it has not been possible to demonstrate in the coronary sinus blood substances having vasoactive or chronotropic action on the coronary circulation or myocardium (Jelliffe et al.). However, coronary flow is markedly increased, coronary resistance and arteriovenous oxygen difference are decreased by short periods of ischemia and by reduction of the oxygen content of the inspired air (Eckenhoff et al., 1947, Green et al., 1942) or by coronary perfusion with reduced blood but without effect on myocardial metabolism, cardiac work, heart rate, or systemic dynamics. The flow increase is about equally divided between decreased extravascular compression and active vessel relaxation (Gregg, 1955).

In addition, active coronary dilatation, with increased coronary flow, about the same arteriovenous oxygen difference, and decreased coronary resistance, follows many dynamic functions of the heart such as increase in systemic blood pressure, cardiac output, cardiac work, heart rate, atrial pressure, and myocardial oxygen consumption. However, the best correlation of coronary flow is with oxygen consumption. This is so because, since normally most oxygen is removed from the coronary blood and the level of coronary sinus oxygen is fairly constant, the increased metabolic demands by the myocardium must be met by increased coronary flow. Therefore, the determinants of coronary flow are also the determinants for oxygen uptake by the heart, and coronary flow must closely parallel oxygen consumption (Alella et al., 1955, 1956, Case et al., 1954, Eckenhoff et al., 1947, Katz, A. M. et al., 1955, Katz, L. N., 1955, Katz, L. N., et al., 1955, Sarnoff et al., 1958b).

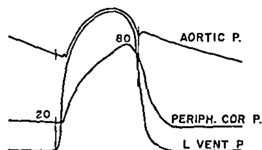
The preceding description suggests that an increase in metabolism (increased oxygen demand) and/or decreased supply of oxygen are the primary antecedents which give rise to active coronary dilatation and increasing coronary flow. It could be that both are effective through a local hypoxia. This general pattern of active coronary regulation together with the indicated passive control is believed to operate in most states of increased stress.

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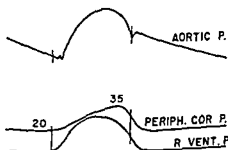
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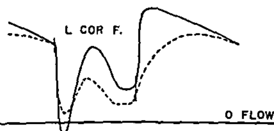
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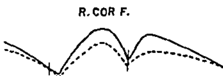
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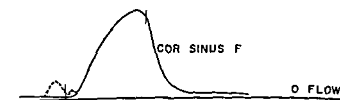


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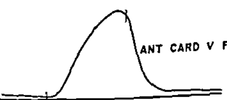


Fig. 2-78. Series of curves relating variations in left and right coronary inflow, coronary sinus, and anterior cardiac vein flow to aortic pressure, ventricular pressure, and peripheral coronary pressure. Coronary inflow (solid lines) obtained with orifice meter, anterior cardiac vein flow also with orifice meter, coronary sinus flow with Pitot tube Broken lines, estimated intramural velocity curves For details see text.

increased coronary flow without change in oxygen uptake When the hemoglobin values reach 6 to 8 Gm, the response of the systemic circulation system is manifested by tachycardia, increased cardiac output, cardiac work, and a fall in peripheral resistance The coronary flow may now triple, coronary venous blood may contain less than 2 vol per cent oxygen, the coronary arteriovenous oxygen difference may be 4 ml or less, and oxygen uptake is considerably increased. The increase in coronary flow is related in part to the decreased blood viscosity and in larger part to the active dilatation associated with myocardial hypoxia, which in turn arises from the low hematocrit and from the increased metabolism Ultimately, myocardial failure will occur in severe anemia when the coronary vessels have approached maximal dilatation and cannot further compensate for the decreased oxygen-carrying capacity of the blood either by increased flow or by increased oxygen extraction. In the presence of coronary stenosis associated with anemia, the effect of coronary arteriolar dilatation in increasing coronary flow is minimized by the high fixed resistance of the stenotic artery, and myocardial depression and failure occur at lesser degrees of anemia (Case et al., 1955, Bing, 1951, Lombardo et al, 1953).

Hormones

THYROID The myocardium participates in the increase in oxygen consumption characteristic of all body tissues in thyrotoxicosis This hypermetabolism is accompanied by an increase in coronary blood flow, a decrease in coronary vascular resistance, and an increase in oxygen consumption per minute and per beat. Since there is an increase in oxygen usage per beat, cardiac oxygen utilization is presumably related not only to the increase in heart rate but to the general hypermetabolism of the myocardium as well (Rowe et al, 1956, Leight et al, 1956)

EPINEPHRINE The response of the systemic and coronary circulations to intracoronary artery injection of a minimal amount of epinephrine is similar to that indicated for stellate stimulation. Probably the coronary changes can be similarly explained With doses of 0 0002 mg or less, coronary flow may increase without any change in blood pressure or heart rate and with an increased coronary arteriovenous oxygen difference With the same or larger doses, as the systemic effects of the substance (increased aortic blood pressure, cardiac output, and changing heart rate) become evident, the coronary effects are exaggerated In those instances in which it has been tested, norepinephrine affects the coronary circulation similarly (Eckenhoff et al, 1947a; Green et al., 1942b). The circulatory responses to cigarette smoking, increased heart rate, systemic blood pressure, cardiac work, left coronary blood flow, oxygen consumption, and decreased coronary vascular resistance, parallel those with epinephrine injection and are presumably related to its release (Schmitthenner et al, Bargeron et al, 1957).

ACETYLCHOLINE (not shown). This hormone, intraarterially, increases coronary blood flow in the anesthetized dog If the dose is properly chosen, this response in the beating occurs without a significant change in blood pressure or heart rate. The increased flow response is completely abolished after atropine. This then increases the mean bore of the coronary vessels, since the flow is elevated in the presence of a normal or lower central coronary blood pressure Its effect on cardiac metabolism has not been determined, and whether its effect is directly on the intrinsic smooth muscle of the coronary vessels or is induced through metabolic changes of the heart is unknown (Eckenhoff et al., 1947a).

PITRESSIN (not shown). Of the hormones used clinically, pitressin alone increases coronary resistance to flow. Coronary flow decreases, the reduction occurring throughout the cardiac cycle in the presence of an increased central coronary pressure It is believed that this drug acts by direct effect on the coronary arterioles, but the possibility of a reduced metabolic influence has not been ruled out (Green et al, 1942b)

Aortic Coarctation

With simulation of clinical coarctation by acute mechanical constriction of the thoracic aorta just beyond the left subclavian artery, venous return to the heart by way of the inferior vena cava is decreased but compensatory flow through various branches of the aortic arch may increase, with a resultant maintained cardiac output and elevated left ventricular work load (Gupta et al) With greater aortic constriction, the net cardiac output decreases, causing the cardiac work to decrease. In either case the coronary dilatation and increased flow arise in large part from active changes in the bore of the coronary bed related to the metabolic demands and in part passively from the increased blood pressure and moderately decreased heart rate (Eckenhoff et al., 1947b, Katz, A. M., et al, 1955) The cardiac oxygen consumption is increased much more by this augmentation of pressure work than with an

RESPONSE OF THE CORONARY CIRCULATION TO PRIMARY STRESS STATES GENERALLY RESULTING IN INCREASED CARDIAC ACTIVITY

In Fig. 2-77 are indicated some of the known responses of the heart and coronary system to various primary stresses. The stresses conveniently divide themselves into those in which the work load of the systemic system is increased or is decreased.

Heart Rate. When the heart rate is increased considerably by electrical stimulation of the myocardium, aortic blood pressure, minute cardiac output, and work increase while the stroke volume and stroke work decrease. Simultaneously, minute coronary flow and oxygen usage increase, coronary resistance decreases, oxygen extraction is unchanged, but the coronary flow and oxygen consumption per beat decrease Since acceleration of the heart means proportionally greater time per beat and per minute in systole than in diastole and since in systole coronary flow is less than in diastole, it would be anticipated that increased heart rate per se should reduce coronary flow Since it does not, it must be that increased flow is due to arteriolar dilatation from the increased metabolic activity. The same trend of flow and oxygen usage per beat and per minute also occurs at the faster heart rate when minute cardiac work is held constant or when comparisons are made at the same stroke work This means that cardiac acceleration can augment the energy metabolism of the myocardium without manifestations of the extra energy as work (Laurent et al., Duff et al)

Transfusion. Augmentation of ventricular load by increasing venous return and hence circulating blood volume through infusion has a clinical counterpart in the load placed upon the human heart by transfusion or by an aorta-caval fistula The increasing coronary flow is partially explainable on a mechanical basis, since the slowing of the heart should increase coronary flow per beat and per minute by increasing diastolic time in which flow is greater However, presumably active dilatation results from the increasing local chemometabolic activity associated with the increased cardiac work. The coronary flow and oxygen are used economically, for the ratio of cardiac work to oxygen consumption increases (Case et al, 1954; Katz, A. M. et al., 1955; Sarnoff et al., 1958b).

Nervous Influences. No critical evidence has been adduced that stimulation of vagal fibers to the heart causes coronary flow changes not explainable on some other basis, such as a change in heart rate. However, *stimulation of the cardiac fibers from a stellate ganglion increases mean left coronary flow as the resultant of a decrease in systolic flow and a large increase in diastolic flow.* Concurrently, left ventricular metabolism, cardiac output, and cardiac work increase while the systolic and diastolic size of the heart decrease. The decreased ratio of pressure to flow indicates *an increased mean coronary bore* (Shipley and Gregg, 1945). The major part of the dilatation is explained by active changes in the coronary bed resulting from the release of an epinephrine-like substance which directly enhances myocardial metabolism This process is very wasteful because the oxygen uptake is greatly increased even when cardiac work is not permitted to rise. The fact that the central coronary pressure and heart rate do not necessarily change rules them out as a necessary part of the flow-controlling mechanisms. About 30 per cent of the flow increase is due to the marked shortening of systole and lengthening of diastole. When the heart rate and blood pressure are elevated, the systemic and coronary effects are greatly accentuated (Eckstein et al, 1950).

Reports have appeared suggesting that coronary flow can be influenced reflexively and adversely by impulses arising in various body regions, especially the heart, lungs, and abdominal viscera, but the importance of these reports is doubtful because of the methodology used (Gregg, 1950, Gilbert et al.).

Exercise (not shown). It would be expected that exercise which increases cardiac work would stimulate the coronary circulation. In man and dog left coronary flow and oxygen consumption increase and the coronary arteriovenous oxygen difference does not change (Essex et al.; Lombardo et al, 1953).

Anemia. The coronary system participates actively in the circulatory adjustments to anemia For hemoglobin values of 10 Gm or more, the systemic circulation is essentially unaltered and the compensation of the coronary system to the decreased oxygen-carrying capacity is similar to that with hypoxia, i e., an

ventricular work (Starzl and Gaertner). In *chronic left heart failure* due to rheumatic, arteriosclerotic, and hypertensive heart disease, the coronary circulation apparently responds by a slight increase in oxygen usage through maintenance of the left coronary flow and an increased coronary arteriovenous oxygen difference. This corresponds with the changes indicated above for the right heart in one stage of failure Such hearts have considerable difficulty in transforming released energy into realizable work. Studies of the coronary circulation in *high-output failure* from excessive *transfusion or a chronic aorta-caval fistula* are not available (Bing et al, 1950, 1951, Lombardo et al, 1953).

Shock. Standardized oligemic shock in dogs is characterized during the hypotensive phase by a decrease in cardiac output, systemic blood pressure, cardiac work, stroke volume, stroke work, and by an increase in heart rate and an adequate central venous pressure Coronary flow and coronary resistance are greatly decreased Coronary flow is generally greater and the resistance generally less than can be accounted for by a simple decline in arterial blood pressure (Opdyke et al, 1947) At the same time, the oxygen uptake decreases and the coronary arteriovenous oxygen difference is generally unchanged (Hackel et al, 1955) The coronary response to sustained hypotension through spinal anesthesia or injection of procaine and Etamon is similar (Eckenhoff et al, 1948, Hackel et al, 1956) With restoration to normal systemic blood pressure by reinfusion (intraarterial and intravenous routes are equally effective—Case et al, 1953), coronary flow is greater and flow resistance is less than at an equivalent arterial blood pressure in the preshock state, and the augmented flow is maintained after circulatory failure subsequently intervenes (Opdyke et al, 1947, Theilen et al).

The fact that early in the hypotensive phase ventricular end diastolic pressure does not rise indicates that the functional capacity of the heart is adequate for the work performed However, that myocardial depression or failure is partially responsible for the hemorrhagic shock syndrome is suggested by the fact that at times after prolonged hypotension there may be evident cardiac dilatation and elevated left and right atrial pressures with the heart eventually proceeding to ventricular fibrillation or standstill. Gross and microscopic evidence of myocardial injury appears in both reversible and irreversible shock. Such myocardial depression could be caused by an insufficient coronary flow during either the hypotensive or the posthemorrhagic periods. The high coronary flow during the restoration period would seem to preclude an inadequate coronary flow as an adequate explanation During the hypotensive period, the actual coronary flow is greatly curtailed The problem is whether the associated sizable reduction in coronary resistance is sufficient to permit enough blood to reach the myocardium to prevent it from failing. In some instances at least, this loss of myocardial contractility is consequent upon an insufficient coronary flow, since the relation of atrial pressure to cardiac size can be reversed by increasing mildly with a pump left coronary flow without change in either the hypotension or blood volume (Sarnoff et al, 1954).

Hypothermia

The circulatory and metabolic adjustments of the heart during hypothermia have been partially explored (Dripps) The associated changes that occur which tend to reduce the coronary flow are a diminution in blood and muscle temperatures, cardiac output, heart rate, cardiac work, oxygen usage by the heart, an increased blood viscosity, and a greatly lengthened period of ventricular systole Opposing these factors are the relaxation of the major coronary vessels, which is known to occur with hypothermia, and dilatation of the coronary bed caused by the hypotension per se. As a resultant of these determinants, coronary flow is decreased at low temperature However, the per cent reduction in cardiac output is greater than in coronary flow, which results in an increase in the coronary fraction of cardiac output at temperatures of 25 to 26°C. There is little change in peripheral resistance in the coronary bed, whereas in the systemic bed an increase in peripheral resistance occurs (Sabiston et al, 1955; Edwards et al, 1954, Berne, Hansen et al). Myocardial function appears to be adequate However, many hearts are apparently not too far from failure, because if total venous inflow occlusion (which decreases coronary flow close to zero) is now added to permit open cardiotomy, myocardial failure

equal increase of volume work following transfusion (Alella et al., 1956). No chronic studies of aortic coarctation have been made, because, owing to development of collateral circuits, the aorta may be first partially and then completely constricted at the arch without permanent development of hypertension proximal to the occlusion In human coarctation not much change is reported in coronary flow and oxygen uptake, but this might be expected because systemic pressure was only mildly elevated (Bing et al, 1949). However, if true, the deviation might be explained by the fact that in these hearts which are hypertrophied, there are fewer capillaries per unit of muscle to carry the oxygen and flow.

Valvular Lesions

Acute elevation of right ventricular pressure by *pulmonary artery constriction* initially decreases right coronary flow, to be followed quickly by a maintained increase in systolic, diastolic, and mean flow in the right coronary artery and, to some extent, in the left coronary artery Upon release, right coronary flow temporarily increases still further During the sustained response, the systemic blood pressure can be fairly well maintained At the same time the right ventricular work declines and its metabolism increases, the former arising from the increased pulmonary artery pressure and cardiac output, the latter from a combination of increased right coronary flow and a greater oxygen extraction from the coronary blood The coronary response to elevation of left ventricular pressure by *aortic constriction* central to the coronary ostia is similar to that with pulmonary artery stenosis In both instances, the sustained flow increase indicates a dominant influence of active coronary dilatation over the increased mechanical flow-inhibiting effect of increasing extravascular compression which earlier was dominant These maintained changes in the coronary circulation could well be the early response in the human being to gradual moderate stenosis of the corresponding valves (Gregg et al, 1943, 1944)

Hypertensive Cardiovascular Disease

An exception to the general picture of coronary compensation to increased systemic stress appears to be the response of the chronically hypertensive heart. In essential hypertension with a normal cardiac output and elevated systemic blood pressure, the coronary flow and oxygen consumption are unaltered while coronary resistance increases. This increased resistance is shared with the renal and cerebral circulations. Since these hearts are generally hypertrophied, total coronary flow and oxygen usage are increased. This deviation is explainable if it is assumed that such hearts with known coronary artery disease have an increased amount of perfused fibrotic tissue (Bing et al, 1950, 1951; Rowe et al., 1955; Lombardo et al, 1957).

Correct values for left coronary flow and myocardial oxygen consumption during natural maximal stress, such as exercise, are not available because of technical difficulties of instrumentation and application. However, the data suggest that with a normal hematocrit and normal arterial oxygen content, maximal work is determined by factors within the muscle and not by limitation of coronary flow and oxygen supply

RESPONSE OF THE CORONARY CIRCULATON TO PRIMARY STRESS STATES GENERALLY RESULTING IN DECREASED CARDIAC ACTIVITY

Heart Failure. The heart shares with other types of muscle the characteristic that an optimum exists beyond which further stretching reduces the force of contraction and leads to myocardial failure. In acute heart failure with progressive deterioration of the myocardium from pulmonary artery stenosis, the changes in coronary flow and oxygen usage per minute and per beat may be in the same direction as those described for the right myocardium but of lesser magnitude If the heart failure is severe enough, extravascular compression can become dominant over any active coronary dilatation from metabolic processes, and coronary flow and oxygen usage may be normal or decrease, with the oxygen extraction at times reaching 90 per cent (Gregg et al, 1943, 1944) The coronary circulation in the heart failing with severe *aortic stenosis* undergoes similar changes When acute heart failure and chronic congestive failure simulating the human condition are induced by surgical complete heart block, changes in left coronary flow and ventricular oxygen consumption also rather closely parallel alterations in the reduced left

3 to 4 weeks, it may approximate normal inflow into that coronary artery, that is, about 30 ml/min. Almost all the collateral flow comes from the unoccluded arteries. The myocardial fibers which were lengthening early after occlusion now shorten in systole. The peripheral coronary pressure which drops early to low values may approximate in pattern and magnitude that in the aorta (Cregg et al, 1939, Blumgart et al, 1950, 1955).

There is some evidence that nature adopts prophylactic measures to protect against subsequent coronary artery occlusion. The coronary vessels appear to be capable of setting up or enlarging anastomoses between themselves without the stimulus of coronary occlusion or insufficiency. Presumably, this is related to some form of antecedent stress. *In the presence of anemia, cor pulmonale, cardiac hypertrophy, or valvular disease, the injectable intercoronary collateral anastomoses in human hearts are increased greatly over those in the normal heart* (Zoll et al, 1951). In the pig, anemia increases the injectable coronary arterial collateral bed (Blumgart et al, 1950, Zoll et al, 1952), in the dog, both chronic anemia and exercise prior to acute coronary artery ligation increase retrograde flow (Eckstein, 1955, 1957). Individuals who escape serious consequences from coronary occlusion may well be those *whose collaterals* have been previously expanded by such means

Early and Late Functional State of the Normal but Overstressed Myocardium. Deletion of contracting muscle blocks following coronary artery occlusion can lead quickly to a reduction in systemic pressure, cardiac output, cardiac *work, and* coronary inflow (Wégria et al, 1954) Evidence indicates that such circulatory failure does not arise from reflex coronary constriction in the nonoccluded coronary artery or from peripheral *muscle vasodilatation* (Gregg, 1950, Opdyke et al, 1948, Levy et al.) Since the retrograde flow does not increase for some hours, any natural compensation must now occur through enhanced action of the normal myocardium Most hearts do respond favorably, but the mechanisms of compensation have not been worked out (Wégria et al, 1954). However, in some hearts, the viable portion of the myocardium may not be in good responsive condition or the same lack of response may occur later after an initial salutary response This is especially apt to happen when occlusion is induced by intracoronary injection of microspheres (Jacobs et al; Bing et al, 1956). Acute or progressive heart failure follows, characterized by a profound hypotension with decreased cardiac output and the clinical signs and symptoms of a shocklike state similar to that which occurs following the loss of blood or plasma. However, circulatory failure not attributable to severe irregularity of the heart beat is presumably not due to peripheral circulatory failure but is due successively to defection of useful contractions in the ischemia area, loss of total contractile energy through expansion of the affected area, and failure of the still viable fractions to compensate adequately. Since experimentally the retrograde flow varies passively with systemic blood pressure and protracted hypotension can at times lead to myocardial damage and failure, attempts have been made to improve such hearts clinically by use of transfusions and vasopressor drugs (Corday et al).

Physiologic Effects of Drugs on Coronary Collateral Function

Drugs known to dilate coronary vessels, such as xanthines, nitrites, and adenylic acid compounds, have not been shown to exert any beneficial influence (increased backflow or muscle shortening during systole) in the ischemic bed within a short time after coronary occlusion (Wiggers et al., 1936) In chronic experiments, cortisone and ACTH do not promote collateral flow or reduce the size of infarcts (Eckstein, 1954, *Wartman et al*) The hypothesis that coronary occlusion reflexively decreases flow in the nonoccluded coronary artery to a fatal level is not borne out by the experimental fact that flow in the *nonoccluded* coronary artery generally rises with coronary artery ligation (Gregg et al, 1950, Opdyke et al, 1948, Wang et al.). The alleged favorable effect on survival of prophylactic and therapeutic drugs, such as papaverine and quinidine, is better explained by their known action in raising the fibrillation threshold and in reducing the *excitability* of the myocardium (Wégria et al, 1942)

A more economical use of the available oxygen or an increased oxygen supply could improve the state of the highly stressed normal myocardium However, the effects of drugs on

supervenes, as evidenced by elevation in mean right atrial pressure and post-mortem findings This trend can be reversed by perfusion of the coronary system with small volumes of oxygenated blood (Lombardo et al., 1957).

THE CORONARY ARTERIAL COLLATERAL CIRCULATION OF THE HEART

The hearts of individuals afflicted with the clinical signs and symptoms of coronary artery disease generally present a dual problem. In the area of the myocardium which is handicapped by sclerosed vessels, the supply of blood and oxygen is too small The remaining area of the heart with a normally functioning coronary system carries much, if not most, of the burden of metabolism and work of the poorly nourished myocardium in addition to its own If the handicapped area of the myocardium is large, then the normal portion of the myocardium is heavily loaded and stressed in its efforts to carry the total performance of the heart.

Early and Late Functional State of Ischemic Myocardium Following Coronary Constriction or Occlusion. Considerable reduction in the lumen of a coronary artery can occur with minimal change in coronary flow This is so because the coronary resistance to flow measured beyond a point of occlusion (by ligation) of a branch of the left coronary artery is considerable, being about 35/20 mm Hg, and the central coronary resistance is quite low (Gregg et al, 1939) The effect of a central constriction on coronary flow is a function of how much the resistance imposed by it is in relation to the resistance in the coronary bed However, obviously excessive central constriction will ultimately decrease coronary flow, resulting in ischemia, which lowers peripheral coronary resistance still further and makes any added central constriction much more effective in limiting flow (Shipley and Gregg, 1944). In part, because of this, the heart has a remarkable ability to retain viability of its muscle beyond a constriction, and significant changes in the electrocardiogram do not occur until coronary inflow is reduced approximately 70 per cent (Wégria et al., 1949).

Despite this, after coronary artery ligation, useful function is lost within a minute in the myocardium normally fed by it, since the muscle mass which was shortening during systole now bulges and lengthens (Tennant and Wiggers). When the peripheral end of such a left coronary artery ramus is opened to the atmosphere, a significant but small flow of arterial blood occurs which can be shown to come from the other nonoccluded coronary artery branches (Gregg et al, 1939). The average retrograde flow of blood obtained from a great many experiments in the author's laboratory approximates 3 3 ml/min from a ligated coronary ramus normally supplying 51 Gm of left ventricle If this collateral flow were not permitted to bleed externally, allowance for the existing mean peripheral coronary resistance of about 25 to 30 mm Hg might reduce the functional backflow to 2 4 ml/min containing 0 5 ml oxygen That a fair portion of this calculated collateral flow actually traverses a capillary bed is evidenced by the fact that the electrocardiogram may improve when the collateral is not permitted to bleed externally. This level of retrograde flow is reached within a few minutes after coronary artery occlusion and does not change for hours During this early period, backflow varies only passively with the systemic blood pressure as the latter is altered by hemorrhage, infusion, and vasopressor drugs. Why the anastomoses function as a set of inert tubes is not known (Gregg et al., 1939, Kattus and Gregg, 1959). This early fixation of function contrasts with the situation in femoral and carotid arteries, where collateral function increases rapidly after occlusion (Eckstein et al., 1941). Loss of viability of the area (absence of local action currents, conduction, or fibrillatory movements) generally occurs within 20 to 60 min, although at times it persists several hours (Wiggers, 1950a). This estimated functional supply of 0 5 ml oxygen is about half that used by 50 Gm of normal resting myocardium Since the oxygen necessary to maintain myocardial viability would be between that for the resting muscle and that supplied by collaterals, viability might be maintained by doubling the existing collateral flow of 3 3 ml and 0 5 ml oxygen

Many hearts are more fortunate collateralwise If fibrillation does not occur and if the heart survives this early period, a considerable but delayed coronary collateral circulation develops. Within 12 hr, the backflow rises significantly, may double within 48 hr, and, with n

Experiment	Procedures prior to ligation of coronary artery ramus	Acute ligation of coronary artery ramus: Mortality	Infarction	Injectable collaterals	Retrograde flow ml./min.	ECG improvement	Persistence of collaterals
Acute	*None*	70%	—	—	3.3 art.	—	—
Chronic	*None*	> 70%	Gross	—	50 art.	—	—
Acute	(Cor sinus constriction or ligation) (Aorta-coronary sinus *shunt*)	↘	—	—	15 ven.	yes	—
Chronic	(Cor sinus constriction or ligation) (Aorta-coronary sinus shunt)	↘	↘	↗	7-12 art.	yes	yes
Chronic	Irritants applied to heart -- Talc, asbestos, mechanical abrasion, mica,phenol, silver nitrate, etc.	↘	↘	↗	5- 8 art.	yes	yes
Beck #1	Mechanical abrasion, asbestos, cor sinus reduced to 3 mm., fat	↘	↘	↗	8 art.	yes	yes
Chronic	Extracardiac tissue applied to heart -- muscle, lungs, intestine, omentum, pedicle skin flap, etc.	↘	↘	↗	—	—	—
Chronic	Artery imbedded in myocardium	↘	↘	↗	2.1 art.	—	Yes
Chronic	Transfused *Anemia*	—	—	—	9 art.	Yes	Yes
Chronic	Severe coronary constriction	↘	↘	↗	27 art.	Yes	Yes
	Severe coronary constriction with *exercise.*	↘	↘	↗	80 art.	Yes	Yes

Fig. 2-79. Physiologic effects of some prophylactic procedures on coronary collateral function in the dog heart.

ventricular efficiency with coronary occlusion is unknown. Drugs such as papaverine, nitroglycerine, epinephrine, aminophylline, Coramine, and khellin do augment the oxygen supply to this area, but whether any one has the desired type of dilatation (active vessel relaxation, decreased extravascular compression, minimal increase in metabolism and cardiac work) has not been established.

Physiologic Effects of Prophylactic Procedures on Coronary Collateral Function.[1] Many investigators have attempted to enhance the coronary artery collateral circulation by surgical means Some of these procedures have been applied some time after a coronary occlusion to selected patients who have had persistent *angina pectoris and gross work disability* Improvements are reported in many instances, especially in the alleviation of pain (Harken et al.; Glover et al, Beck et al., 1955). As with drugs, the yardstick of the success of any of the maneuvers should be a considerable reduction in mortality rate and in the number and size of infarcts, an increase in the anatomic and functional collaterals, and improvement in the electrocardiogram These parameters are difficult to evaluate in human beings. The physiologic effects of some of these prophylactic procedures on coronary collateral function in the dog heart are set forth in Fig. 2-79.

Ligation of a major ramus of the left coronary artery in the open-chest dog causes a high mortality rate within the first few hours Chronically, there is considerable infarction When *partial or complete occlusion of the coronary sinus* or *creation of an aorta-coronary sinus shunt* precedes coronary artery ligation, the immediate mortality is reduced considerably and a considerable retrograde flow of coronary venous blood occurs (Eckstein et al, 1954) Chronic coronary sinus ligation, arterialization of the coronary sinus, application to the epicardium of mechanical and chemical irritants and of various types of extracardiac tissue, including embedding a patent artery if they precede coronary artery ligation, generally reduce mortality and infarction, increase the anatomic and functional collaterals and improve the electrocardiogram. Accordingly, it is deduced that these surgical maneuvers give sustained, and in the case of the coronary venous maneuvers, immediate protection against ligation of a major coronary artery branch. The retrograde flow equals or exceeds that estimated to be necessary to maintain viability (Baronofsky et al.; Beck et al, 1935, 1941, 1948, 1955, Bloomer et al, Moran; Sabiston et al., 1957; Vineberg et al).

[1] Therapeutic attempts have also been made to create a new blood supply to the potentially infarcted area by anastomosis of a systemic artery or plastic tube to a coronary artery beyond its point of constriction or occlusion Such a bypass not only affords a new blood supply but also on theoretical grounds might additionally improve it, because the increased length of the anastomosis would retard the arterial pulse so that it arrives during diastole, the period of greatest flow (Fig 2-79). This procedure has not been fully developed or finally evaluated experimentally (Absolon et al. Kantrowitz et al.).

Cardiac benefit from these procedures could arise from retrograde flow of blood from the superficial veins through the capillary bed, from development of inter- and extracardiac collaterals, or from elevation of the ventricular fibrillation threshold, thus giving nature time to develop additional collaterals to sustain the heart There are no critical experiments to prove that with the acute coronary venous maneuvers, protection against fibrillation and death is supplied by blood flowing in a retrograde direction from coronary vein to capillary, to ventricular cavity. Acute perfusion of the coronary sinus with arterial blood at or near aortic blood pressure, or acute ligation of the coronary sinus, results in venous congestion of the left heart with an increased coronary venous pressure, at times equal to the aortic pressure, a diffuse myocardial hemorrhage (with the exception of the septum which remains pink in color), and a sizable reduction in left coronary inflow and cardiac output When the peripheral portion of the occluded coronary artery is permitted to bleed externally, the measured backflow is of highly reduced blood and the volume is increased greatly (to 15 ml or more) over that which occurs with acute coronary artery ligation alone (Gregg and Dewald, 1938a, b) It is very important to know that this blood can be shown to have traversed the capillary bed of the occluded coronary artery in a reverse direction However, proof is lacking that when the ligated coronary artery is not permitted to bleed externally, flow from the superficial coronary veins is diverted through the capillary bed of the left myocardium and then into the left ventricular cavity Actually, the development of extreme myocardial embarrassment, together with the fact that most of left coronary artery inflow and the blood entering the coronary sinus from the shunt can now be recovered in the anterior cardiac veins of the right ventricle, offers not quite certain evidence that

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Cerebral circulation

SEYMOUR S. KETY

Physiologic studies in lower animals have yielded much information concerning the fundamental physiology of the cerebral circulation More recently, the *nitrous oxide method* has made similar information available for the normal and diseased human brain By means of this technique, which represents an application of the Fick principle to a nonmetabolized but freely diffusible substance, a mean value has been obtained for the cerebral blood flow in healthy young men close to 54 ml/100 Gm/min, corresponding to a value of *740 ml/min for a brain of average weight* The normal cerebral oxygen consumption is found to approximate 3 3 ml/100 Gm/min, or 46 ml/min, for the whole brain *Thus, this organ, representing 2 per cent of the body weight, normally receives about one-sixth of the cardiac output and consumes 20 per cent of the oxygen utilized by the body as a whole at rest*

The rate of cerebral blood flow depends upon the two factors which regulate the circulation in any part of the body, although each of these may in turn be the result of a host of other variables The two factors in terms of the cerebral circulation are the *pressure gradient*, or difference between the arterial and venous blood pressures at head level and, secondly, the so-called *cerebral vascular resistance*, representing all those factors which hinder the flow of blood through the vessels of the brain.

Recent investigation does not substantiate the earlier belief that cerebral blood flow passively follows changes in arterial blood pressure Studies in intact human beings have strengthened the concept that a normal arterial blood pressure is zealously maintained by numerous homeostatic mechanisms, such as the carotid sinus reflex and central control of peripheral vascular tonus, and that, as long as the mean arterial blood pressure remains above a critical minimum level, *cerebral blood flow is actually regulated intrinsically by changes in cerebrovascular resistance.* The critical level of blood pressure below which cerebral circulation is likely to be reduced appears to be of the order of 70 mm Hg; below that value, there is a progressive decrease in blood flow paralleling the decrease in blood pressure Above 70 mm Hg, there appears to be no correlation between blood pressure and cerebral blood flow. The cerebral *venous pressure* ordinarily plays a minor role in regulating both the pressure gradient and the cerebral blood flow. Even in congestive heart failure, whatever slight changes in cerebral circulation may occur are more likely to be the result of other factors than the moderate increase in venous pressure Under *gravitational stress*, however, the venous pressure at head level may become an important determining factor in cerebral blood flow Studies on man in the centrifuge have shown that cerebral circulation may be adequately maintained, for a while at least, at accelerative forces of 4 to 5 *g*, even at a time when the arterial pressure at head level is only a few millimeters of mercury Under these circumstances, the hydrostatic forces operating upon the arterial and venous side of the circulation equally reduce the venous pressure to as low as −60 mm Hg and, thus, maintain the arteriovenous gradient

Aside from the considerations previously dis-

the deep ventricular drainage channels are not used. The observation that these procedures may elevate the ventricular fibrillation threshold suggests but does not prove that this is a major mechanism of protection.

In hearts with chronic application of various maneuvers, protection in large part and in many instances is probably afforded by the augmented collateral circulation. For example, with an aorta-coronary sinus shunt, the backflow of 10 to 12 ml of arterial blood exceeds that calculated to be necessary for viability and persists for at least a year and even after closure of the shunt On the other hand, no significant change occurs in coronary sinus flow with application to the heart of a chronic pedicle skin flap or carotid artery implant, indicating that in these instances backflow does not traverse the capillary bed when it is not permitted to bleed externally. Since most hearts following coronary artery ligation die within 24 hr, since the usual retrograde flow observed with these procedures is rather small, and since sham operations at times give sustained protection against coronary occlusion, the possibility must be seriously entertained that the benefits to the heart of reduced mortality and infarction arise, in part at least, from the protection which the procedures themselves might give against ventricular fibrillation in the presence of coronary occlusion (that is, without an immediate increase in retrograde flow), thus giving additional time for collaterals to develop and sustain the heart.

In summary, in the normal heart, a moderate collateral circulation exists which functions immediately following coronary artery occlusion Different prophylactic procedures are successful experimentally in preserving life either by compensating for a deficit in the supply of collateral oxygen or by preventing ventricular fibrillation, thus giving collaterals time to develop. This protection against occlusion of a coronary artery is associated with a collateral development on the arterial side of the order of magnitude essential for viability.

The rationale of the use of these procedures in human beings remains to be determined. There is no question that some of these procedures have been helpful, especially in the relief of cardiac pain. Those surgical procedures which protect the dog heart against subsequent coronary occlusion by augmenting the collateral circulation might also protect the human heart similarly if used prophylactically. However, positive benefit to human beings with occlusive coronary artery disease would not necessarily be on this basis. In the laboratory, artery ligation is always preceded by a surgical maneuver, whereas, in the human being, there is time after acute coronary occlusion for natural maximal collateral development before the surgeon tries to augment it.

cerebral vessels, while the inhalation of 100 per cent oxygen is associated with a mild vasoconstriction in the brain Several atmospheres of oxygen pressure are associated with an even greater increase in cerebrovascular resistance.

Since cerebral metabolism is associated with both a decrease in oxygen tension and an increase in carbon dioxide tension in the tissue, both of which are powerful dilators of cerebral vessels, it is highly likely that these chemical effects upon cerebral vessels play an important role in the adaptation of the cerebral circulation locally to local metabolic needs

In addition to the normal products of metabolism, *a wide* variety of drugs appear to exert some effect upon the tonus of cerebral vessels. Among those which decrease cerebrovascular resistance and, presumably, dilate cerebral vessels, should be listed *histamine* and *papaverine*, while contrary to the usual belief, *aminophylline* and *caffeine* appear to exert a significant constrictor effect on cerebral vessels The effects of *epinephrine* have been the subject of some controversy Much of this may have been the result of the presence in natural epinephrine of two substances plus the varying roles of anesthesia and species differences in observations performed *on animals In* man, the effects of intravenously administered pure substances such as *l*-epinephrine and *l*-norepinephrine are relatively clear-cut When these materials are injected by continuous intravenous infusion at a rate adjusted to maintain a rise in blood pressure of approximately 25 per cent, it is seen that *l-norepinephrine behaves as a cerebrovascular constrictor*, increasing cerebrovascular resistance even more than it raises blood pressure, with a concomitant slight but significant reduction in cerebral blood flow *Epinephrine*, on the other hand, appears to have no striking effect upon cerebral vessels While there is no significant change in cerebrovascular resistance, the cerebral blood flow increases, presumably as the result of the increased blood pressure brought about by this drug. Thus, the ability of a drug to cause an increase in cerebral blood flow in therapeutic dosage is not entirely dependent upon its vasodilator properties, and *histamine*, which does indeed decrease cerebrovascular resistance, produces no change in cerebral blood flow because of the parallel decrease in mean arterial blood pressure which accompanies its administration. *Papaverine*, however, appears to affect cerebrovascular resistance to a greater extent than it affects the mean arterial blood pressure, thus achieving a *significant increase in* cerebral blood flow. Substances like *alcohol* in moderate dosage, or *nicotinic acid in dosage sufficient to* produce facial flushing, *do not produce a significant* change in cerebrovascular resistance or cerebral blood flow in man.

In *essential hypertension*, there occurs an increase in cerebrovascular resistance which is parallel to the increase in blood pressure, resulting in the maintenance of a normal cerebral blood flow The nature of this increase in tonus of cerebral vessels remains obscure, although it is probably similar to that which occurs in other vascular beds in this condition Blockade of the cervical sympathetic chain on both sides does not alter this high cerebrovascular resistance, indicating that it is *not* mediated through the known sympathetic innervation to the *head* It is interesting that, whatever its cause, the increased cerebrovascular resistance found in essential hypertension is capable of relaxation in association with a fall in blood pressure achieved by a variety of techniques, including blockade of the thoracolumbar sympathetic outflow and the use of a large number of hypotensive drugs

cussed, however, the regulation of the cerebral blood flow is achieved largely by *local factors* which hinder the flow of blood through the brain and which, taken as a whole, comprise the cerebrovascular resistance

The *intracranial pressure* would be expected to exert an effect upon the thin-walled vessels of the brain, increasing the resistance to flow in a manner similar to that which obtains in the familiar Starling resistance model This has been shown to occur in man, where a good linear correlation is found between intracranial pressure and cerebrovascular resistance The cerebral blood flow, however, does not always decrease in high intracranial pressure, since compensatory rises in blood pressure often diminish the effects of the intracranial hypertension alone.

The *viscosity of the blood* is another component in cerebrovascular resistance, although major changes in viscosity are achieved only by fairly marked alterations in the erythrocyte concentration. In *severe anemia,* there is associated with a decreased erythrocyte hematocrit a significant fall in cerebrovascular resistance accompanied by an increase in cerebral blood flow Conversely, in *polycythemia vera,* where the viscosity of the blood may increase markedly, there is a great increase in cerebrovascular resistance and a marked reduction in cerebral blood flow. In fact, in this condition, the lowest values for cerebral blood flow are often found. Although other factors, such as tissue carbon dioxide and oxygen tensions, may contribute to the changes in cerebrovascular resistance found in these conditions, there is little doubt that physical viscosity must also play an important role

By far the largest share of the control of cerebrovascular resistance resides in *the state of narrowing or dilatation of the cerebral vessels themselves,* either on a structural or a functional basis

Arteriosclerosis narrows the bore of cerebral vessels and is associated with a significant increase in cerebrovascular resistance. In fact, this function shows a progressive increase with age, which may be related to the increasing incidence of arteriosclerosis. In meningovascular syphilis, the perivascular cuffing seen histologically may be responsible for the increase in cerebrovascular resistance found by physiologic measurement.

The *tonus* of cerebral vessels is capable of marked variation under the influence of neurogenic and chemical factors. Intracranial vascular nerves are known to parallel the cerebral vessels throughout the brain and appear to take origin from certain nerve plexuses, notably one which invests the internal carotid artery. This plexus receives a constrictor input from the cervical sympathetic chain and a dilator input by way of the greater superficial petrosal nerve which emerges from the cranium along with the facial nerve. The constrictor and dilator properties of these two supplies, respectively, have been demonstrated in experiments on animals. Their role in man remains to be established No demonstrable effect was observed on cerebral circulation or cerebrovascular resistance upon bilateral procain blockade of the stellate ganglia, even though this was associated with obvious signs of sympathetic paralysis in the face and eyes This strongly indicates the absence of a significant tonic vasoconstrictor effect on cerebral vessels generally from the cervical sympathetic chain

The *humoral* or *chemical influences* upon the tonus of cerebral vessels are the most powerful and probably account for the greater part of normal cerebrovascular control Cerebrovascular resistance is exquisitely sensitive to the *carbon dioxide tension* in arterial blood, showing a marked increase with hyperventilation and an even more marked decrease with the inhalation of carbon dioxide in 5 or 7 per cent concentration That these effects must be the result of constriction or dilatation of cerebral vessels is shown by the absence of any change in viscosity of the blood or an appropriate alteration in intracranial pressure Since both hyperventilation and the inhalation of carbon dioxide are associated with corresponding changes in hydrogen ion concentration in the blood, it is difficult to decide, on the basis of such observations alone, whether it is the carbon dioxide or the hydrogen ion which is responsible for the dilator effect. However, the intravenous infusion of sodium bicarbonate, which is associated with an increase in bicarbonate ion and a decrease in hydrogen ion concentration in the blood, also produces what appears to be a dilatation of cerebral vessels, so that an increased acidity is not necessary to cerebrovascular dilatation.

Hypoxia, like *hypercapnia,* appears to dilate

ing, out to the pulmonary branches, except that the amount of smooth muscle in the wall progressively increases. Arteries with a diameter ranging from 1 to 0.1 mm have a prominent media of circularly arranged smooth muscle between the internal and external elastic laminae. The walls of arterial branches less than 0 1 mm in diameter consist essentially of poorly supported endothelial tubes which abruptly break up into a profusely anastomotic capillary network Thus, there are no vessels corresponding to the muscular arterioles of the systemic circulation The alveolar capillaries are the principal structural element lining the alveoli The capillary network may open up and dilate to such an extent that the space between the capillaries surrounding the alveoli is less than the diameter of a capillary (Liebov et al)

Bronchial Circulation and Collateral Circulation of the Lungs. The single pulmonary ar-

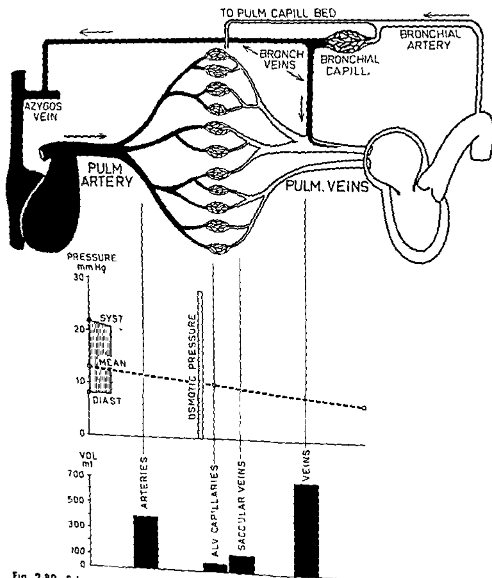


Fig 2-80 Schematic representation of the double vascular supply of the lungs Only the main connections between the pulmonary circuit and the bronchial circulation are included Below, the average pressures in the pulmonary circuit of normal man are plotted as measured relative to the atmospheric pressure The black columns, drawn from data (modified) given by Bazett and Bord, represent estimated volumes of blood contained in different parts of the pulmonary circuit. The values apply to a normal, hypothetic man, weight 75 kg, assuming a total blood volume of 6 liters

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Pulmonary circulation

HILDING BJURSTEDT

The systemic and pulmonary vascular systems may be regarded as two open circuits, connected in series to form a closed loop with two separate pumps, the right heart and the left heart. The two pumps deliver the same volumes of blood per unit of time, if compared during any prolonged period, although short-lasting output differences occur under certain conditions.

There are important differences between certain characteristics of the two systems: (1) The systemic circulation is a high-resistance circuit with a large artery-vein pressure gradient, and the left heart acts as the "pressure pump" while the pulmonary circuit offers very slight resistance to the flow from the right heart ("volume pump"). (2) The pulmonary circuit conducts blood to and from only one type of tissue (alveolar membranes), which makes the need for vasomotor control of blood distribution in the circuit less obvious than in the systemic circulation. (3) It is a relatively short, large-caliber, and distensible circuit, in which the vessels subdivide rapidly and in which the volume of blood is much smaller than in the systemic circulation. (4) The pulmonary arteries and veins are essentially exposed to the normally subatmospheric intrathoracic pressure, the "base line" of both the systemic and pulmonary circulation; its variations, e.g., during respiration, greatly influence the hemodynamics of the pulmonary circulation because of the low pressures in the vessels. (5) To serve the principal function of the lungs, that of gas exchange between the surrounding atmosphere and the venous blood, the pulmonary capillaries are exposed to the alveolar spaces; consequently little, if any, external counterpressure is exerted by the surrounding lung tissue.

It has been said that the lesser circulation is a miracle of structural simplicity and a nightmare to the student of integrated function. While the first part of this statement is open to question, certainly much darkness still has to be dispelled to permit a coordinated understanding of the mechanisms involved in, for example, the hemodynamic interplay of the systemic and pulmonary circuits, and in the integration of pulmonary circulation and ventilation for optimal gas exchange. Our present concepts of the functional characteristics of the pulmonary circulation make it mandatory to include the ventilatory factor on a par with the pulmonary. The realization of this need has in part prompted the great current interest in various functional aspects of the pulmonary circulation (Bjurstedt, 1957).

ANATOMIC BACKGROUND

The branches of the pulmonary arterial tree follow the arborization of the bronchi rather closely. The tip of each terminal branch of the artery is in close proximity to a bronchiole. After further successive subdivisions, the alveolar ducts are connected to the alveolar sacs, which are embraced on all sides by a network of pulmonary arterioles and capillaries. Gas exchange between the pulmonary airways and blood may occur in all divisions beyond the bronchioles. Pulmonary venules drain the capillaries of the alveolar sacs and merge into larger veins, in which arterialized blood flows to enter successively the interlobular and the pulmonary veins.

The walls of the main arteries and their branches structurally remain unchanged, although narrow-

fective pulmonary arterial pressure increases (Hamilton et al, 1953). However, in view of the great distensibility of the pulmonary circuit, it is likely that increased resistance to flow contributes to the last-mentioned effect. That the total pulmonary resistance is slightly increased by lung inflation is borne out by experimental observations, as well as theoretic considerations Thus, if the intrathoracic (or pericardial) pressure is used as reference zero pressure, the average tissue pressure, which may be termed the *intramural pressure of the lungs*, is always *positive* in the intact, normal body Furthermore, as the intrapulmonic-intrapericardial pressure difference increases during inspiration, as is the case during lung inflation, however produced, the intramural pressure surrounding any given portion of the pulmonary vascular bed must increase This is the same as to say that the external pressure acting on the pulmonary vessels increases during inspiration, if referred to the pericardial pressure surrounding the right heart Since this would tend to diminish the distensibility of the vessels during inflation, the increasing intramural pressure would thus appear in the hemodynamic picture as an increasing resistance against outflow from the right heart (Fig 2-81)

If this concept is correct, normal active inspiration, and also passive lung inflation in the intact body, are accompanied by an increase in the resistance against outflow from the right heart, mainly because the lung volume is increased It follows that pressure breathing, artificial positive-pressure respiration, and the Valsalva maneuver will obstruct the pulmonary vascular bed no more than will the same degree of lung inflation produced by normal inspiration.

In the "tamponade" effect, which may occur with high intrapulmonary pressures, the stopped flow in the pulmonary circuit depends more on defective filling of the right heart than upon pulmonary resistance. Even during mild positive pressure, prolonged, deficient filling may become a danger factor, both in open-chest surgery and in artificial respiration performed on the intact body. The decreased abdominal muscle tone during general anesthesia permits venous pooling in abdominal vessels, and so contributes to circulatory failure by diminishing the venous return to the heart Such pooling would seem to be facilitated also by unconsciousness from other causes and by curariform drugs

During active *straining against a closed glottis*, the systemic arterial pressure is raised initially because the high intrathoracic pressure is added to the pressure caused by the contractions of the heart, the sum being transmitted peripherally along the arterial tree The effective right atrial and pulmonary arterial pressures are slightly decreased because of displacement of blood into venous channels outside the trunk, which impedes venous return to the heart. Straining may, if prolonged, de-

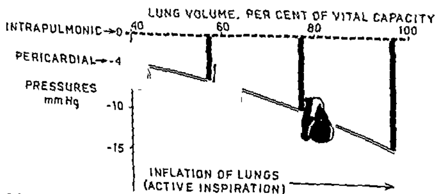


Fig 2-81. When the lungs are inflated by active inspiration, the external pressure acting on the heart (pericardial pressure) decreases along the double line. During normal quiet inspiration the intrapulmonic pressure (broken line) remains approximately constant and equals the atmospheric pressure The average intramural pressure of the lungs, i e, the pressure acting on the exterior of the pulmonary vessels (see text) increases with the pericardial-intrapulmonic pressure difference (black columns) and thus increases the resistance to outflow from the right heart (H Bjurstedt Pulmonary Circulation)

tery follows each branch of the bronchial tree but yields it no branches until the first alveoli appear in the walls of the respiratory bronchioles. Whereas pulmonary arteries are end arteries, the bronchial artery, after originating from the aorta or an intercostal artery, soon forms a plexus with at least two major branches, joined by many laterals distributed within the bronchial walls. These arteries supply oxygenated blood to the bronchial tree as far peripherally as the bronchioles.

Normally, blood brought to a lung via the bronchial arteries may follow three courses in returning to the heart (Fig 2-80). In the proximal two-thirds of the major bronchi, some of this blood is brought *via the azygos veins to the right atrium,* while more distally in the bronchial tree drainage is *into the pulmonary veins,* which thus carry small amounts of non-oxygenated blood It is apparent that most of the drainage from the bronchi is into the pulmonary veins (Liebov et al.). It is, however, well recognized that the bronchial veins are poorly developed and inadequate to accommodate more than one-third of the blood delivered by the bronchial arteries in unit time, the rest is taken care of by *connections* with the pulmonary circuit *Microscopic vascular* communications between the bronchial and pulmonary arterial systems at the capillary level have long since been described in the normal lung (Bruner and Schmidt) After interruption of the pulmonary artery and in various pathologic states, these channels reach macroscopic proportions. How much of the blood from the bronchial arteries, if any, normally reaches the walls of the alveoli themselves is not known Functional anastomoses between pulmonary and bronchial arteries, but not between pulmonary veins and bronchial veins, have been demonstrated (Shedd et al). On the other hand, functional capillary and venous anastomoses are present to a certain extent in the visceral pleural circuit, which drains in the pulmonary veins (Bruner and Schmidt).

BLOOD FLOW THROUGH THE PULMONARY CIRCULATION

Resistance to Blood Flow through the Pulmonary Circuit

Since there are no high-resistance muscular arterioles in the pulmonary circuit, no abrupt fall in the pressures occurs in the small vessels of the lungs. The distensible vessels of the circuit appear to be passively expanded in response to greatly increased flow with no or very little increase in the pulmonary arterial pressure. Normally the pulmonary artery–left atrium pressure gradient amounts to an average of some 10 mm Hg (Cournand, 1950). The comparatively short and large-caliber vessels of the circuit give a low hindrance ($= 8/\pi \times l/r^4$, where l and r = the length and radius of a vessel, respectively), the effect of which is a total average resistance to flow roughly one-tenth of that in the systemic circulation

CAPILLARY FLOW. The volume pulse in the pulmonary arteries is visible on fluoroscopy, and Lee and Du Bois have demonstrated beyond doubt that it continues beyond the capillary beds. By using Krogh's nitrous oxide technique with the subject sitting in a body plethysmograph, they were able to calculate instantaneous pulmonary capillary flow events by reading the pressure fluctuations in the plethysmograph. This demonstrates in an ingenious way that the capillary blood flow is highly pulsatile (peak blood flow at rest about 12 5 liters/min, slowest flow about 3 liters/min, moderate exercise yielding a peak flow of about 28 liters/min). These observations do not imply, however, that all the pulmonary capillaries blush with each heart beat The enormous changes in flow rate confirm that the pulmonary capillary and arteriolar system must be very easily distensible; whether this is passive or depends upon critical opening pressures is as yet open to question

CHANGES IN RESISTANCE DURING NORMAL RESPIRATION AND DURING INCREASED INTRAPULMONARY PRESSURE. Because the reference pressures for intrathoracic vascular channels are not precisely known, intrathoracic circulatory dynamics, even during normal respiration, is not thoroughly understood However, by using the intrathoracic or intrapleural pressure ("the base line of the circulation") for intrathoracic hemodynamics, one arrives at the following picture (for more details as to pressure measurements in the pulmonary vessels, see below). It is now firmly established that normal inspiration causes an increase in the filling, or "net," pressure of the right heart by way of the increased negativity of the intrathoracic pressure This has often been referred to as the *abdominothoracic pumping mechanism,* which permits an increased pressure gradient along the large veins An increased outflow from the right ventricle into the pulmonary arterial tree consequently results during inspiration Accordingly, the ef-

istence of a nervous control is given by the reactions to pulmonary emboli. Thus, glass beads injected into the right ventricle cause pulmonary vasoconstriction from powerful intrapulmonary reflexes (Niden and Aviado). Likewise, embolization with small quantities of barium sulfate suspension may lead to vastly increased pulmonary vascular resistance in heart-lung-head preparations, which can be prevented by hexamethonium and by previous sympathetic denervation (Price et al.)

Inhalation of gases with low oxygen tension have been shown by von Euler and Liljestrand (1946) to produce increased resistance to blood flow in the pulmonary circuit. A pressure rise was observed in the pulmonary artery in the cat, which was independent of (1) an increase in blood flow, (2) increase in pressure of the left atrium, or (3) extrinsic nervous control of the lung vessels. This local effect was therefore considered as part of a special *intrinsic mechanism*, by which a low regional O_2 tension in the lungs would result in the shunting away of blood to better-ventilated alveoli. These observations of increased pulmonary vascular resistance during low O_2 inhalation have later been shown to be valid also for normal man (Motley et al.). It has furthermore been reported that if low O_2 tension is confined to one lung, blood flow through this lung is diminished and is instead diverted into the "high-oxygen" lung. The reactions of the pulmonary circulation to low O_2 tensions are rather brisk and marked, if compared with response to vasoactive drugs, such as epinephrine, ergotamine, and hexamethonium. Since these drugs may affect the pulmonary circulation indirectly through their actions on the left heart and systemic circulation (which may actually exaggerate the response of the pulmonary artery pressure), their true effects on the pulmonary vessels may preferably be studied with the left ventricle replaced by a mechanical pump.

FUNCTIONS OF THE PULMONARY CIRCULATION

The pulmonary circuit simultaneously performs three major functions. (1) It permits exchange of gases (O_2, CO_2 and N_2) between the alveolar spaces and the blood, this is its principal function. (2) It constitutes a variable-capacity system for optimal supply of blood to the left heart. (3) It acts as a filter for various types of emboli carried from the systemic veins and the right heart.

The Perfusion Factor in the Pulmonary Gas Exchange

In passing through the alveolar capillaries, the blood is spread out in a thin layer so as to come in direct contact with the alveolar spaces. The total area available for respiratory gas exchange is normally around 90 m², the layer of blood being about 10 μ thick. The area over which blood is exposed to the alveolar air can increase when metabolism increases, as in exercise. Roughton has estimated that the time spent by a given blood particle in contact with the alveolar air is 0.75 sec at rest, 0.34 sec during exercise. As noted above, the flow through the capillaries is highly pulsatile.

Assuming with Comroe and his associates (1955) that total alveolar ventilation and total pulmonary flow are normal, and that the only problem is whether air and blood are uniformly distributed to different parts of the same lungs, the distribution of flow within the lung tissue is equally important for the efficiency of gas exchange within a given region of lung tissue, as is its ventilation. This is evident from the fact that if total alveolar ventilation and pulmonary blood flow were normal, but all the ventilation went to one lung (no perfusion) and all the blood flow went to the other lung (no alveolar ventilation), the patient would quickly die of asphyxia. Variations in ventilation/perfusion ratios less extreme than this probably occur normally, and certainly occur in many patients with cardiovascular disease. Such variations probably represent the most frequent cause of hypoxemia in clinical medicine. The important point is whether the same ventilation/perfusion ratio exists in all parts of the lungs or not. If it does, the blood will be maximally arterialized for given levels of total ventilation and perfusion. In an "ideal" lung, every alveolus has a ratio of 0.8, and the contact area is sufficient to allow full arterial O_2 saturation.

Uneven distribution of blood within the lung [illegible]

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Uneven distribution of blood within the lung tissue will cause variations in the ratio, unless ventilation is readjusted regionally to match the increased or decreased blood flow If this ratio varies from one alveolus to another, less O_2 is taken up by and less CO_2 is removed from the blood passing through the lungs The effects of varying ratios must be examined separately for O_2 and CO_2.

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The reasons for this are as follows. The effects on uneven distribution of flow on the O_2 uptake is to cause an increased alveolar-arterial O_2 gradient. This is understandable, since overventilated (underperfused) regions cannot to any appreciable extent increase the O_2 saturation in the blood leaving these regions because of the flat top of the O_2 dissociation curve; conversely, underventilated or overperfused regions are not able to raise the O_2 saturation of the blood to full extent. The result is that the mixed arterial blood is less saturated with O_2 and similar to that of a direct shunt of blood from pulmonary artery to pulmonary vein Both types of shunts may conveniently be grouped under one category and termed *venous admixture* Both these are now believed to exist even in normal individuals.

As to the CO_2 elimination, a decreased ventilation/perfusion ratio in a certain tissue region cannot materially increase its CO_2 *output*, since venous blood CO_2 tension is normally only 6 mm Hg higher than the mean alveolar or arterial tensions In regions where the ventilation/perfusion ratio is higher, less CO_2 is blown off than normally. A combination of these two situations must result in a decrease in the CO_2 removal from the blood, the effect being the same as that caused by an increase in the anatomic dead space Since this hypothetic increase is not in the airways, but is due to nonuniform ventilation/perfusion ratios within different lung regions, it has been termed "alveolar dead space" or "parallel dead space" (Fig 2-82)

The net effect of regional changes in the perfusion of lung tissue, as outlined above, *is essentially to cause a decreased O_2 saturation* in the mixed arterial blood A concomitant rise or drop of the mean arterial CO_2 tension does *not necessarily occur*, since a normalization is, within limits, brought about by automatic adjustment of the total effective ventilation through the controlling action exerted by the respiratory centers Compensatory chemoreflex hyperventilation caused by deficient oxygenation of the arterial blood from venous admixture is, however, not sufficient to equalize the alveolar-arterial O_2 gradient, owing to the peculiar shape of the O_2 dissociation curve *This is the reason for hypoxemia in diseases of the lung with anatomic or physiologic shunts*, the latter being caused by, for example, atelectasis, local edematous infiltration, or emphysema

For the study of the significance of the perfusion factor in the pulmonary gas exchange during a variety of conditions, the reader is advised to consult the O_2-CO_2 diagram, as outlined by Rahn and Fenn.

Hemodynamic Functions of the Pulmonary Blood Volume. The blood volume contained in the lungs has attracted much interest, especially as to its role in the distribution of blood of the body in various situations Current concepts concerning the regulation and function of pulmonary blood volume in health and disease have been based mainly on theoretic considerations and indirect evidence rather than direct measurements, the latter having been restricted on account of the technical difficulties involved. The amount of blood in the pulmonary circuit in normal subjects at rest and in the recumbent position has been estimated by most investigators as between 20 and 30 per cent of the total blood volume (Sjöstrand, 1953). Measurements with the aid of the Stewart-Hamilton formula (pulmonary blood volume = cardiac output × circulation time through the lungs), in conjunction with scintillographic tracing of albumin labeled with I^{131}, have yielded a mean value of 1.240 ml, corresponding to some 28 per cent of the total blood volume for *normal man at rest in the recumbent position* (Lammerant). The volumes of blood contained within various parts of the pulmonary circulation are illustrated at the bottom of Fig 2-80.

In the erect posture, the heart and lungs supply much of the blood needed to fill the orthostatic limbs. Sjostrand (1935) found that an average of more than 600 ml blood was displaced from the lower extremities to the rest of the body in five subjects *shifting from the standing to the reclining position*. Five hundred milliliters were taken up by the thorax, and most of the remainder by the arms, hip, head, and neck Only a few milliliters went to the abdomen Of the 500 ml taken up by the thorax, the pulmonary vascular bed takes up 3 ml for every milliliter taken up by the heart chambers Positive-pressure breathing, instead, causes a displacement of blood from the thorax An increase of pulmonary pressure of 30 cm water *displaces 500 ml in the supine* subject, or about half the blood contained in the lungs; in the standing position, there is less blood in the lungs and the amount which can be displaced by pressure breathing is correspondingly less Conversely, negative-pressure breathing of 20 cm water draws blood in the lungs and heart, as judged from decreased vital capacity of the lungs.

On the basis of such findings, it is apparent that blood is easily transferred to and from the heart and lungs in various situations. The blood accommodated in the pulmonary circuit appears to be distributed diffusely in the lungs.

The major part may go to the venous side, where postcapillary sinusoids have been described, which apparently are capacious enough to accommodate large quantities of blood. The capillaries may also contribute to the circuit capacity for blood. However, Roughton, by determining the pulmonary capillary blood volume from exchange of carbon monoxide, obtained a figure of only 60 ml for subjects at rest and 96 ml for individuals doing heavy work. These figures, which have not been seriously questioned, refer to the amount undergoing active respiratory gas exchange in the alveoli.

CORRELATIONS WITH HEMODYNAMIC EVENTS. From the readiness with which blood is transferred to and from the pulmonary circulation, *it can be inferred* (1) that the circuit constitutes a relatively distensible part of the cardiovascular system, and (2) that there must be an interplay with other distensible parts These are to be found mainly in the systemic collecting veins, and to a certain degree in the systemic arterioles and capillaries For an understanding of this interplay, it may be useful first to consider some established correlations between the pulmonary volume and certain hemodynamic events The amount of blood available to maintain the filling pressure during diastolic inflow in the left heart appears to vary directly with the pulmonary blood volume This is borne out by investigations of changes in stroke volume with the distribution of blood during anesthesia and with changes in the body position The pulmonary blood volume seems also to be a determining factor for the stroke vol... [illegible]

... [illegible] legs These and *many other observations seem to demonstrate that the amount of blood on the venous side of the pulmonary circuit is one factor controlling the filling of the left ventricle and consequently the stroke volume, at rest as well as during muscular exercise*

PULMONARY BLOOD VOLUME AS A HEMODYNAMIC RESERVE The pulmonary circuit has in the past been referred to as a *reservoir*, in which blood is held on tap within a part of the vascular system where it can be used for direct supply of the left heart when a larger cardiac output is rapidly called for. The contained amount of blood has been regarded as a "blood depot" or a "blood store," similar to that in the dog's spleen However, these terms seem untenable, since they give the impression that the pulmonary blood volume is at times *excluded* from the *total* active circulation There is no evidence for such an assumption, even if certain fractions of this volume have a slower circulation than others within the circuit. It may be pertinent at this point also to emphasize that "capacity" should not be *confused* with the contained blood volume. They are certainly identical in one sense, because empty spaces cannot exist within the vessels. Capacity, however, has a different meaning and denotes "what there is room for"; i.e., it must be defined in relation to pressure when dealing with distensible vessels Since the pulmonary vessels normally contain blood under pressure, their volume in the fully relaxed state must be greater than the contained blood volume

It is evident that the pressure on the venous side of the pulmonary vascular bed is an important factor in the maintenance of the necessary filling pressure for the left ventricle. The distensibility of the vasculature (= the reciprocal of its volume elasticity coefficient), which varies with vasomotor influence, is, however, not the only decisive factor. The actual amount of blood contained in the pulmonary vessels determines the *constancy of the filling pressure.* If the available blood volume is small, the filling pressure may be high enough at the beginning of diastole, but will rapidly fall during the rest of the inflow. The filling thus becomes inadequate for high output from the left heart If, on the other hand, the available pulmonary blood volume is large and the vascular distensibility great, the filling pressure may be visualized as having a high degree of constancy during diastole but as being too low for adequate filling

Little is known as to the mechanisms by which the filling pressure is kept at an optimal level with a high degree of constancy. Unfortunately there is as yet no method of measuring the variability in the capacity of the pulmonary circuit, which has to be expressed in terms of changes in its pressure-volume curve Vasomotor reflexes and alterations in the external counterpressure of surrounding tissues presumably act to control its distensibility. *The extent to which such changes occur to keep up the filling pressure of the left heart is,* at best, *incompletely known*

One may be justified in regarding, with Sjostrand (1952, 1953), the pulmonary blood volume as a *hemodynamic reserve* that is at

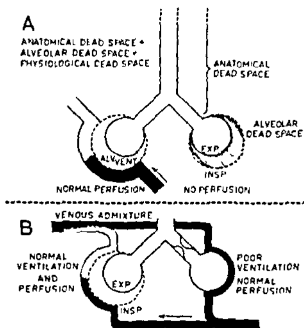


Fig. 2-82. A. Components of dead space. *Circular areas represent individual alveoli.* Absent perfusion of ventilated alveoli (right) creates an alveolar dead space (regionally increased ventilation/perfusion ratio). B. Venous admixture from poor ventilation of alveoli with normal perfusion (regionally decreased ventilation/perfusion ratio). The carbon dioxide tension of mixed arterial blood may be kept near its normal level by automatic adjustment of total ventilation effected through the respiratory centers. Decreased oxygen saturation of mixed arterial blood from venous admixture cannot, however, be elevated to full saturation by hyperventilation, even with inhalation of 100 per cent oxygen. This is because the peculiar shape of the oxygen dissociation curve prevents compensatory "superarterialization" of blood in better-ventilation regions (H. Bjurstedt *Pulmonary Circulation*)

no time excluded from the total active circulation. The distensible circuit serves to cushion transient discrepancies in the outflow from the two ventricles of the heart until a new hemodynamic equilibrium is reached, e g , in rapid changes from the standing to the reclining position. It constitutes an extension of the systemic low-pressure system, the function of which is to maintain an optimal effective circulating blood volume under varying conditions Bearing in mind that this is brought about by (1) the effective central venous pressure at the level of the right atrium, and (2) the distending blood volume available for the filling of the right heart, the supply mechanism being similar to that described above for the left heart, one has to assume a rather precise interplay in the vasomotor control of the distensibility of the systemic veins and the pulmonary circuit, respectively. For instance, after a steady state has been reached in the effective circulating blood volume during motionless standing, vasomotor influence, by restricting the capacity of the systemic veins, compensates for the hydrostatic displacement of blood to the legs so as to maintain an adequate filling of the right heart. This requires that the capacity of the pulmonary circuit becomes adjusted, so that the stroke volume of the left heart is kept identical with that of the right heart Adjustments in the capacities of the two parts of the low-pressure system are also required during muscular exercise. There is a major difference between the two situations, however, since in the latter case we have systemic arterial and capillary dilatation in the muscles which greatly increases the capacity of these vessels. The systemic arterial pressure cannot be maintained unless the outflow from the right heart is increased, which in turn requires that a substantial volume of blood be taken from the low-pressure system. Its capacity consequently has to be diminished to keep up the effective filling pressure for the right heart

In summarizing, there are two variable-capacity portions of the low-pressure, distensible system, which are connected in series. the systemic veins and the pulmonary circuit. Both portions contain blood volumes which partake in the total active circulation as *hemodynamic reserves* for circulatory adjustments when redistribution of blood in the body is needed (Fig 2-83) These adjustments primarily occur in order to maintain adequate filling pressures for the heart at all times regardless of the position of the body, the magnitude of total blood volume, the redistribution of blood in dilated, systemic capillary beds, or the accumulation of blood in distended dependent veins. There is substantial evidence that the *pulmonary reserve* plays a strategic role as an immediate source of blood to meet any sudden demand for increased cardiac output

Filter Action of the Lungs. Provided that there is no open, right-to-left shunt, the pulmonary network acts to check foreign bodies, thrombi, air bubbles, or fat particles which have entered the blood stream on the venous side of the circulation This filter function is

important, because these emboli might otherwise occlude systemic arteries supplying vital organs, such as the brain or heart, and cause tissue necrosis. Fortunately, the lungs are particularly adapted to filtering out vascular plugs by virtue of their double circulation, which allows the bronchial circulation to take over the supply of blood to the lung region shut off from the pulmonary arterial tree (Fig 2-80) *Lung tissue is, therefore, rarely destroyed by obstruction of the pulmonary blood supply*, but survives while the embolus is resorbed or recanalized, after which the tissue may resume its function in the gas exchange This process may occur repeatedly during life without producing symptoms unless the embolus is large or is located in a critical position

An extensive *collateral circulation may develop as a result of obstruction of the pulmonary artery or its branches* Such collateral circulation with large *anastomosis of the bronchial with the pulmonary arteries can be induced in the dog by ligation of the pulmonary artery*, a gradual improvement in the ability of the collaterals to carry large quantities of blood may permit them to accommodate about one-third the output of the right ventricle at the end of 18 months (Liebov et al)

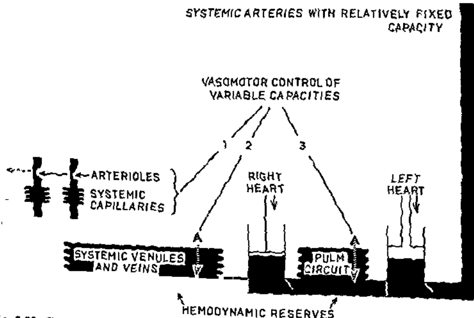


Fig. 2-83. The capacities of the two parts of the low-pressure *system* (2 + 3), respectively, are *automatically regulated*, according to current *theory*, so that the pulmonary blood *reserve is utilized for sudden increase* in *cardiac output* Both reserves (2 + 3) are used to *permit* an increase in the capacity of the *systemic arterioles* and capillaries (1) as, for example, in muscular exercise (H Bjurstedt Pulmonary Circulation.)

Respiratory influences on cardiovascular function

DOMINGO M. AVIADO, JR.

For anatomic reasons, there is a reciprocal dependence between the respiratory and circulatory systems. The functional reasons for the interrelationship between the two systems are complex, since they involve several aspects of cardiovascular physiology and of respiratory physiology This chapter will review them in terms of the cardiovascular effects of hypoxemia, one outcome of respiratory insufficiency

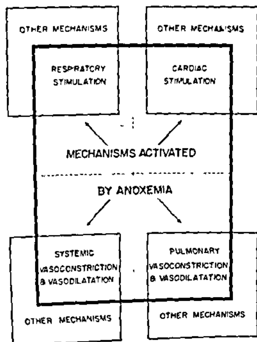


Fig. 2-84. Composite diagram for figures 2-85 to 2-88 showing the four conspicuous effects of anoxemia. Each effect can be aroused by mechanisms other than those participating during anoxemia.

Hypoxemia is the most suitable example because it has been investigated more extensively than other manifestations of respiratory disturbances (hypercarbia, acidosis, ventilatory insufficiency, etc.).

The general plan is to discuss briefly four conspicuous effects of hypoxemia, viz: (1) respiratory stimulation, (2) cardiac stimulation, (3) systemic vasoconstriction and vasodilatation, and (4) pulmonary vasoconstriction and vasodilatation For each of these four effects, the responsible mechanisms (nervous, humoral, or otherwise) will be analyzed Each of these four effects will also be discussed in terms of other mechanisms, not related to hypoxemia, that participate in various functional abnormalities of the respiratory system (Fig. 2-84).

RESPIRATORY STIMULATION (*Fig.* 2-85)

Aroused by Hypoxemia. The hyperpnea of hypoxemia arises entirely from activation of *chemoreceptors* in the carotid and aortic bodies This fact has been adequately established by animal experiments showing that after denervation (ninth and tenth nerves), hypoxemia becomes a depressant to the respiratory center (Schmidt) The respiratory stimulation seen during hypoxemia does not require further comments, outside of indicating that the chemoreceptors are also responsible for bringing about most of the cardiovascular effects of hypoxemia

Accompanying Pulmonary Congestion. The dyspnea accompanying engorgement of the

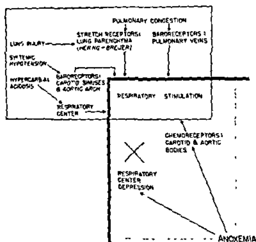


Fig 2-85. Mechanisms for respiratory stimulation

lung vessels is not due to hypoxemia because it is not seen constantly The respiratory difficulty is regarded to be predominantly a *neurogenic response arising from the congested lungs* Two sets of pulmonary receptors are probably sensitized or stimulated by congestion, viz the *Hering-Breuer stretch receptors* and the *pulmonary venous pressoreceptors* (Aviado and Schmidt, 1955) These two sets of receptors are conspicuously different from each other, the former is sensitive to volume changes of the lungs *and affects* exclusively respiration, whereas the latter is sensitive to changes in pulmonary venous pressure and affects respiration and systemic blood pressure. There are other sets of receptors in the lungs with exclusive effects on circulation which will be discussed below All these reflex mechanisms exemplify the nervous mechanisms by which primary disturbances in the lungs extend to involve respiratory and circulatory control

CARDIAC STIMULATION (Fig 2-86)

Aroused by Hypoxemia Like the hyperpnea of hypoxemia, cardiac stimulation also arises from stimulation of chemoreceptors The observed increase in cardiac output seen during hypoxemia is directly due to tachycardia and to increased force of cardiac contraction The accompanying hyperpnea probably contributes indirectly to the increase in cardiac output by increasing the venous return, as an exaggeration of the normal thoracic pump mechanism After denervation of the carotid and aortic body chemoreceptors, the cardiac effects of hypoxemia are not clear. It appears that the local myocardial depressant action of oxygen lack may be overshadowed by the stimulant effects of hypoxemia on the adrenal medulla and on the medullary cardioaccelerator and cardioinhibitory centers (Neil and Heymans, Chap. 12).

Accompanying Systemic Hypotension. The tachycardia that accompanies systemic arterial hypotension is more difficult to explain, particularly if it is the immediate outcome of acute injury to the lungs (Clemedson) The most obvious cause for the tachycardia is a reflex from the pressoreceptors in the carotid sinuses and aortic arch When aortic pressure is reduced, there is diminished inhibitory activity from these pressoreceptors, resulting in tachycardia There is of course the possibility that receptors in the lungs can contribute to reflex changes in heart rate, particularly if the injury results in local irritation of the receptors in the lung vessels, trachea, and pleura (Aviado et al., 1957)

During the *Valsalva maneuver*, the tachycardia can be explained on the basis of a rise in intrathoracic pressure interfering with venous return to the right side of the heart and causing a reduction in systemic arterial blood pressure After release of the high pressure, the systemic pressure overshoots, and there is marked bradycardia The increase in stroke volume contributes to the overshoot, but it has been suggested that the rise in pressure also results

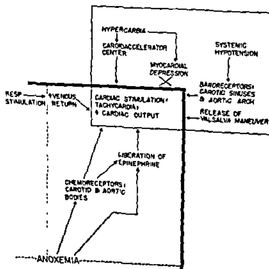


Fig. 2-86. Mechanisms for cardiac stimulation.

Fig. 2-87. Mechanisms for systemic vasoconstriction and vasodilatation.

from reflex vasoconstriction (Sharpey-Schafer). If the vasoconstriction were arising from the pressoreceptors in the carotid sinuses and aortic arch (exposed to low arterial pressure during high intrathoracic pressure), this would be concomitant with a slowing of the heart rate This would be paradoxic because pressoreceptor mechanisms either stimulate or inhibit the cardioaccelerator and vasoconstrictor mechanisms together, rather than exert the opposite effect

SYSTEMIC VASOCONSTRICTION AND VASODILATATION (Fig 2-87)

Aroused by Hypoxemia. The various systemic vascular beds behave in two different ways during hypoxemia The blood vessels of the *kidneys, splanchnic area,* and *limbs* are reflexly constricted during hypoxemia, also by activation of the chemoreceptors The *coronary* and *cerebral vessels* do not constrict but instead become dilated, partly because of their weak vasomotor supply, and partly because of their greater sensitivity to the local dilatation from hypoxemia (Kety and Schmidt, 1948; Green and Wégria). The local effects of hypoxemia on these vital organs are similar to those of hypercarbia, so that the combined result of both arising from any respiratory insufficiency will improve circulation to the heart and brain

Aroused by Pressoreceptors. The same organs that are reflexly constricted by hypoxemia are similarly constricted by a reduction in blood pressure at the various pressoreceptor areas. These include the carotid sinuses, aortic arch, left ventricle, right atrium, and pulmonary veins. The functional significance of the first two is generally known, but the information on the others is incomplete. Several foreign chemical agents have been shown to stimulate them, but their role in specific diseases of the lungs, if any, is unknown (Dawes and Comroe).

PULMONARY VASOCONSTRICTION AND VASODILATATION (Fig. 2-88)

Aroused by Hypoxemia. The similarities in the general behavior of the systemic and pulmonary vessels include their response to hypoxemia The lung vessels are reflexly constricted, humorally constricted, but locally dilated during hypoxemia (Lilienthal and Riley, Cournand, 1955). The combined outcome of these vascular effects and the concomitant cardiac stimulation is *pulmonary arterial hypertension.* There are earlier reports that hypoxemia can locally constrict pulmonary blood vessels (Nisell, Duke, 1956), but recent experiments show only local dilator response (Aviado et al., 1957) The confusion is probably related to differences in techniques and will be resolved by further experimentation

Aroused by Pulmonary Embolism. The effects of *experimental embolization of the lungs* consist also of combined constriction and dilatation The lung vessels are mechanically occluded by the emboli, are reflexly constricted (reflexes from embolized to nonembolized lobes), and humorally constricted (by sero-

Fig 2-88. Mechanisms for pulmonary vasoconstriction and vasodilatation

tonin, histamine, or both). The site of constriction is not yet known but appears not to involve the arteriovenous anastomoses which have been observed to open during embolization (Niden et al.). If a similar mechanism happens in human lungs, the opening of the shunts may serve to exaggerate the hypoxemia but, at the same time, serve to protect the right ventricle from an extremely high pulmonary pressure. All these pulmonary vascular mechanisms require further exploration, because they appear to be important in the pathologic physiology of various pulmonary diseases (fibrosis, emphysema, primary pulmonary hypertension, pulmonary edema, etc.)

SUMMARY OF INTERRELATIONSHIPS BETWEEN RESPIRATORY AND CIRCULATORY SYSTEMS

The effects of respiration on cardiovascular function can be summarized as follows

1 Respiration can alter *venous return*, which is reflected in fluctuations of blood pressures in the aorta, pulmonary vessels, and the various chambers of the heart These fluctuations are seen during normal respiratory movements and become exaggerated during hyperpnea of hypoxemia, dyspnea of pulmonary congestion, continuous positive-pressure breathing, and the Valsalva maneuver

2. *Primary diseases of the lungs* may interfere with pulmonary blood flow to the extent of interfering with the uptake of oxygen during circulatory stress Although most of the interruption to flow is due to organic lesions of the pulmonary vessels, there are powerful nervous and humoral constricting mechanisms which may hasten the onset of failure of the right ventricle.

3 *Interference in adequate oxygenation of blood in the lungs* can result in reflex stimulation of the heart and constriction of some blood vessels The latter response to hypoxemia would result in shunting of blood from the less vital areas (kidneys, splanchnic, and extremities) to the more vital organs that undergo local vasodilatation (coronary and cerebral). The chemoreceptors of the carotid and aortic bodies are responsible for such a compensatory mechanism If these receptors were absent, the circulatory system would rapidly fail when respiration is threatened

7

Renal circulation

HAROLD LAMPORT

The function of the kidney is essentially to preserve the quality of the circulating blood by selectively removing from it solutes and water which otherwise would accumulate. Thus, it serves an important role in homeostasis. The kidneys participate in maintaining the acid-base balance of the blood and in synthesizing ammonia, thereby conserving mineral base. Hormones influencing primarily the blood vessels of the body are secreted by the kidney, which also responds to hormones elaborated elsewhere. In addition, the renal circulation participates importantly in the control of the systemic circulation.

The formation of an ultrafiltrate in the glomeruli is purely *a passive circulatory effect*, but the elaboration of urine from the crude filtrate and the remaining concentrated plasma involves *delicately adjusted metabolic activity of renal tubular epithelium*. Such activity requires the circulation of oxygenated blood but also depends heavily on the physical factors underlying diffusion and flow. An understanding of its circulation is necessary for those interested in any of the functions of the kidney.

The extrinsic factors influencing renal circulation are neural activity, the characteristics and concentration of constituents of arterial blood (including hormones and drugs), and the pressures in the renal artery, vein, ureter, and abdomen.

The intrarenal factors affecting circulation through the kidneys are the hemodynamic consequences of its unique vascular anatomy (still in dispute), hormones secreted by the kidney, the influences of the elaboration of the urine on the volume and pressures and perhaps the composition of the several fluids involved, and possibly the activity of an intrarenal nerve plexus.

RENAL VASCULAR ANATOMY[1]

Before 1940, there was little dispute about the salient facts of normal mammalian renal vascular anatomy. Then, Trueta and his coworkers offered experiments to demonstrate that blood flow to the outer cortex was in large part "shunted" to the cortical-medullary zones under reflex neural and hormonal vasoconstriction resulting from extremely stressful systemic procedures. Blood diverted through the "juxtamedullary" glomeruli comprising the "Oxford shunt" was reported to flow next into vasa recta, which descend deep into the medulla alongside loops of Henle and collecting tubules and then return to the subcortical zone. A portion of this diverted blood is supposed to enter the arcuate veins without having passed through a second capillary net. As man possesses polylobular kidneys, the term "arcuate" or "arciform vessels" is thought to be a misnomer (Trueta et al.). The Oxford group's views have not been widely accepted outside England. Their injection studies have been criticized (Insull et al.), and their belief in the interdependence of cortical and medullary circulation is considered hemodynamically unsound, a change in either circulation of less than 11 per cent resulting only from *maximal* change of the other (Lamport, 1950). An authoritative review concluded that even a partial shunt was improbable (Berstrand).

The possible existence of arteriovenous broad-channel shunts in the renal parenchyma has aroused speculation since the description of Ludwig's arteriole. Oliver's dissections suggest that such channels may develop in Bright's disease with the degeneration of a glomerulus into a single, non-

[1] See also Part 1, Chap. 11. *Editor.*

filtering vessel. Injection of glass beads down to 19 μ in size into renal arteries fails to confirm the normal existence of important noncapillary arteriovenous communications. Trueta doubted their existence (Heggie, Bradley, 1957). However, preferred channels larger than true capillaries, similar to those described elsewhere (Zweifach, 1949), have been described in the glomerulus and peritubular capillaries (Hall).

The hypothesis that a high proportion of the red cells in renal blood normally flows through as yet unidentified vessels with a shorter circulation time than plasma has been raised and will be discussed below (Pappenheimer et al., 1956).

Swann and his group emphasize the presence of constrictions of hemodynamic significance in the arcuate and interlobular veins in dogs and man and refer to other investigators (Barrie) who regard such constrictions in the medulla to be erectile tissue, also providing arteriovenous shunts.

NORMAL RENAL BLOOD FLOW

The activity of the kidneys, like that of the heart, is approximately proportional to body surface area. Homer Smith, weighting reported data, gives average resting renal blood flow at 98.5°F rectal temperature per 1.73 m^2 as 1,166 ml/min for men and 940 ml/min for women. An average of 19.4 per cent of the plasma is *filtered* in the glomeruli and then almost completely resorbed in tubules. *Renal blood flow is about one-fifth of resting cardiac output* despite the kidneys' small size. Essentially, the kidneys are almost an arteriovenous aneurysm.

The *erect position* and exercise *decrease* renal blood flow. Pregnancy, if uncomplicated, has *surprisingly* little effect on kidney circulation. A high-protein diet augments both renal blood flow and filtration in the dog, but response in *man* is smaller and less dependable. A low-*protein diet in essential* hypertension slowly *reduces* kidney blood flow only if salt has been restricted, *increased* salt consumption and water *diuresis* are normally uninfluential (H. W. Smith).

Measurement of kidney blood flow in man until recently depended on the presumption that the plasma clearances of certain substances, primarily Diodrast and sodium para-aminohippurate (PAH) at low concentrations are consistently related to flow (H. W. Smith). PAH is superior to Diodrast in not diffusing into red cells (Bradley, 1957). The kidneys extract about 91 per cent of the PAH flowing through them (H. W. Smith). Only a portion of the remaining 9 per cent is thought to be in blood supplying nonparenchymal parts, such as capsule, calices, pelvis, and fat. It seems that there are unidentified, nonsecretory blood channels in the kidney which under unusual experimental circumstances, carry a larger proportion of the circulating plasma than otherwise. They account for the finding that the extraction ratio of PAH is not altogether fixed. Renal vein catheterization via a small vein and the vena cava in man now permits more exact measurements of renal plasma and blood flow using the Fick principle. The essential validity of human renal blood flow estimation from PAH clearance has been confirmed (Bradley, 1957).

EFFECT OF ARTERIAL PRESSURE ON RENAL BLOOD FLOW

Suggestions that *arterial pulsation* may be of importance in the kidney have not been borne out experimentally: renal blood flow, filtration, and the excretion of water and electrolytes are unaffected by converting pulsatile pressure to the equivalent integrated mean steady pressure (Berliner, 1954, Selkurt, 1951).

Blood flow through the kidney in various species is remarkably independent of variation in the level of arterial pressure, a fact which has not yet been satisfactorily explained and has recently prompted much *experimental study* and conjecture (Selkurt, 1955). The filtration rate is maintained even more constant than flow up to 250 mm Hg. Below about 80 mm Hg, flow and filtration rate fall with *arterial* pressure. But *from 80 to 200 mm Hg, flow rate increases only slightly*. Systemic factors are unimportant (Haddy et al.); the pump-lung-kidney preparation shows *almost intact* autoregulation (Winton, 1956). It must be concluded that the stability of renal blood flow depends on an *intrinsic renal mechanism*.

Autoregulation within the kidney may be the result of active smooth muscle constrictors in the vascular walls which respond to *pressure*, flow, or intrarenal vasodilating substances, and are either autonomous or *reflexly* dependent on a neural plexus (De Muylder; Bradley, 1957). Recently, Pappenheimer (1956) has proposed a purely physical cell-separation theory in order to account for autoregulation, *the fall* of PAH extraction ratio with declining hematocrit, and the reportedly low concentration of red cells compared to plasma (*the* "dynamic hematocrit") in the kidney when contrasted with that in the blood of large vessels.

The theory applies the long-known fact that red cells of blood flowing rapidly through small arteries and arterioles move in the faster axial stream, leaving the plasma to flow more slowly in a sleevelike region along the vessel wall (Lamport, 1955). A small arteriole branching from a larger vessel, particularly if its orifice does not jut into the central lumen, skims mostly plasma, leaving the axial red cells to go on Thus, the interlobular arteries, on this theory, would supply *cell-poor blood to the afferent arterioles of the juxtamedullary glomeruli and a cell-rich blood to those nearer the capsule in the cortex.* The theory also requires the existence of as yet unidentified, small-volume, postglomerular shunts not supplying secreting epithelium and through which red cells rather than plasma pass preferentially When blood pressure is raised, flow is augmented and, according to Pappenheimer (1956), the separation of cells from plasma is thereby enhanced. The ensuing decline in viscosity of the cell-poor moiety to the plasma-skimming afferent arterioles of glomeruli near the medulla is slight, proportional to the fall in the already low hematocrit. However, arterioles near the capsule now receive cell-rich blood of still higher hematocrit When the cell content is high, blood viscosity rises disproportionately faster than the hematocrit, so that the pressure increase has caused cortical glomeruli to receive blood the viscosity of which has been considerably augmented The result, according to this theory, is that the integrated effective viscosity of blood flowing from the interlobular arteries is increased with blood pressure Renal blood flow therefore rises little with increasing arterial pressures, not because of compensating vasoconstriction, but because of compensating increased effective blood viscosity

Bradley (1957) accepts intrarenal axial streaming of red cells but regards the evidence for its significance in autoregulation as inconclusive. The investigators of Augusta, Ga , find no sharp reduction in renal circulation time for red cells compared to plasma, agreeing with Lilienfeld et al., and report that autoregulation persists in transplanted kidneys maintained on oligocythemic (below 15 per cent), hemoglobin-containing oxygenated blood (Waugh, Green, J.). Thus, these workers regard autoregulation as a vital response of renal vasculature, perhaps slightly augmented by the effects of red cell separation. Pitts and his co-workers found no evidence for autoregulation in severely anemic dogs (Thompson et al., 1957). Haddy et al. found that renal autoregulation resulted from autonomous active vasoconstriction in response to pressure rather than flow. The failure of autoregulation in the vasoconstricted kidney after blood pressure recovery from massive hemorrhage conforms with their views (De Wardener et al). That autoregulation is not invoked by elevated venous pressure also argues against a physical origin related to flow. Selkurt's valuable review (1951) astutely points to the 1- to 2-min time delay in autoregulation as signifying an active response.

The author's own impression of this moot subject is that cell separation plays little role in autoregulation but that it may well explain the decline in PAH and Diodrast extraction ratio with oligocythemia, if nonsecretory red cell–preferring shunts exist as postulated. Hall's anatomic observations already cited may point to the needed routes (see also Part 1, Chap 11). The effects of injected serum albumin in man (marked increase in plasma flow, decrease in filtration fraction but rise in filtration rate, fall in extraction ratio with no fall in tubular excretory capacity) lead Homer Smith to concur in the existence of arteriovenous, nonsecretory shunts preferentially opened by the intravenous albumin. Other evidence points in the same direction (Bradley, 1957; Winton, 1956). Autoregulation, with the evidence at hand, especially the finding by Brull et al that cocaine derivatives in the perfusing blood abolish it, appears to be an *active reflex effect mediated through an intrarenal, neural plexus.*

The whole question of differences in activity and hemodynamics among the population of glomeruli and their tubules is being reexamined Evidence increases that disparity among nephrons is considerable and will better explain renal responses (Winton, Bradley, 1957) Under certain assumptions, 95 per cent of nephrons are said to handle glucose within ±40 per cent of the mean for the kidneys (Smith) However, in the dog, glucose excretion shows little variation among nephrons (Kessler et al.).

EFFECT ON RENAL BLOOD FLOW OF VENOUS PRESSURE

In trained dogs, the pressure in the renal vein is 7 to 9 mm Hg. Swann and his associ-

ates have pushed catheters as far as possible into the renal venous tree. They obtain a "wedge" pressure of around 25 mm Hg, which falls suddenly to about 7 mm as the catheter tip is withdrawn from the interlobular veins (Koester et al). This work has been confirmed in man, in whom the intrarenal venous pressure drops suddenly from 17.7 to 5 6 mm Hg, the site being close to the arcuate veins (Brun et al) Corresponding anatomic constrictions in the veins, some variable in degree (being activated by arterial pressure, as is erectile tissue elsewhere in the body), have already been mentioned Elevation of renal vein pressure reduces renal blood flow and filtration proportional to the reduction in perfusion pressure (Selkurt, 1955). Chronic experimental renal venous obstruction, however, does not reduce flow (*Share*)

EFFECT ON RENAL BLOOD FLOW OF URETERAL PRESSURE AND TISSUE PRESSURE

The *exact interrelationship* between ureteral (*i e.*, renal pelvis) tissue and venous pressure is *still not clear* Winton (1956) equated the least increase in one of these *parameters* to produce an observable fall in urine flow under rather artificial conditions, but these views are no longer accepted Since both blood and urine flow through collapsible channels surrounded by kidney tissue, a *large rise in* one of these three (renal venous, tissue, and ureteral pressure) will be *communicated* to the other two,

[illegible] are presumed to be low (Swann) The pressure in the *renal* pelvis is *essentially intra*-abdominal pressure Elevating *ureteral pressure* has no effect on renal *circulation* and function in acute dog *experiments* until it exceeds 20 mm Hg, whereupon blood flow declines with further rise in ureteral *pressure*, filtration rate falling even more (*Share*)

Renal venous, tissue, and *ureteral* pressures increase along with intraabdominal pressure As a result, *increased intraabdominal pressure reduces kidney blood flow in man and experimental animals* more than the *same level of ureteral* pressure (Share).

Direct measurement of intrarenal pressure by insertion of *needles* connected to sensitive manometers or pressure-balanced for zero flow has not evoked agreement. Swann and his associates, using hypodermic needles in dog kidneys, found intrarenal pressures of about 25 mm Hg, close to their finding for interlobular venous pressure, and rising directly with venous pressure once it was raised to this level. It responded less closely to arterial pressure. Gottschalk et al found values of 10 mm Hg with micropipets in the kidneys of cats, rabbits, guinea pigs, and rats, in which *pressures* are more uniform than in the dog, where they found 16 mm Hg Puncture of tubules and capillaries gives *pressure values higher than* those recorded for interstitial pressure (Winton, 1956)

The hypodermic needle is admittedly *an* enormous crowbar causing *massive micro*scopically apparent damage. Since the distensibility of the kidney is extremely slight, sixteen *times less* than that of the liver (the lowest of four other organs cited by Winton), this author concludes that needle puncture methods measure a *high* dynamic pressure balance between bleeding into and absorption from a venous hemorrhage He argues for an interstitial pressure of 10 mm Hg in the dog.

EFFECT ON RENAL CIRCULATION OF THE CHARACTERISTICS OF THE BLOOD

Just as the kidney circulation and filtration *rate* are remarkably stable under arterial pressure variation, so are they intrinsically stable, but to a lesser degree, under acute variation *of the cell content* of the blood and the plasma concentration of water, oxygen, and carbon dioxide (Winton, Thompson, Smith; Selkurt) *Chronic* anemia in man reduces renal *plasma* flow and filtration moderately, but blood flow falls markedly because of the low hematocrit. *After* treatment, normal values are restored The extraction ratio is *unaffected, in contrast to that in* acute oligocythemia. Experimental chronic polycythemia in dogs produced *the* opposite effects (Berliner) *Infusion of salt*-*poor* albumin, already cited, raises blood osmotic pressure and *viscosity*, and sharply *increases* renal plasma flow. Filtration rises less *precipitously*, and extraction falls (*Smith*)

Local heating of the kidney has *little effect* on its circulation (*Smith*) Blood *flow in* the *isolated, perfused* kidney falls with temperature and is proportional to the *rise* in blood viscosity. *At 4°C*, where vital *responses are*

abolished, little pressure autoregulation persists, in the author's estimation.

EFFECT OF NERVES ON RENAL CIRCULATION

The nerve supply to each kidney is of *sympathetic* origin, running in the homolateral splanchnic nerves from T4 to L2. No function other than vasoconstriction has been demonstrated (De Muylder; Peon; Smith).

Denervation of a dog kidney sensitizes it to adrenergic hormones and drugs. But in essential hypertension, this is not the case. Normally, at rest, there appears to be little tonic activity of the renal nerves, they become active in systemic circulatory adjustments. The kidney is important in the control of blood pressure, since it passes more than a fifth of cardiac output.

Stimulation of renal nerves markedly reduces blood flow, filtration rate, and urine output Since sympathetic activity usually releases epinephrine, neurohumoral responses are superimposed on purely neural vasoconstriction Denervation of the kidney is difficult to accomplish completely. It does not produce hyperemia and does not much diminish autoregulation of renal flow and filtration.

Chronic, sinusoidal stimulation of renal nerves at frequencies of 2 to 4 per second appears to produce long-lasting *renal* vasoconstriction and hypertension, to be discussed later (Kottke et al). Renal blood flow is reduced only initially

The possibility that intrinsic autoregulation of renal circulation may be *integrated* by a neural plexus involving pressoreceptors has not been positively demonstrated, but may be the case. The extensive "neurality" of renal vasculature, especially the veins, has been stressed (De Muylder)

RESPONSE OF RENAL CIRCULATION TO HORMONES AND DRUGS

The kidney does not demonstrate reactive hyperemia. Its circulation may respond reflexly to drugs or hormones, which stimulate its extrinsic innervation, or, secondarily, to their effects on its secretory activity. Some of these substances act directly on the kidney vessels (or their intrinsic innervation).

Epinephrine and *norepinephrine* markedly reduce blood flow through the kidney while leaving filtration rate essentially unchanged The kidney swells during this vasoconstriction, possibly as a result of increased venous tone *Angiotensinase* (*renin*), *angiotensin*, *Paredrinol*, *VEM*, and their analogues behave like the adrenergic group. *Pitressin* and *histamine* do not produce consistent effects. *Ether* and *cyclopropane anesthesia*, if lightly administered and without an operation, produces little change in renal circulation. Deeper anesthesia depresses it. *Pyrogen*, *magnesium sulfate*, and *hydralazine* augment renal blood flow (Bradley, 1957). Vasodilatation occurs as a result of a few hypotensive drugs, such as *reserpine*, but mostly these drugs do not much change the circulatory rate, probably because of autoregulation.

The kidney itself produces the circulatory active *angiotensinase* (*renin*), an enzyme precursor of *angiotensin*, and VEM (vasoexcitatory material), which sensitizes metarterioles to epinephrine (Smith). VEM is neutralized by *ferritin* (of hepatic origin) during hypoxia The kidney may produce other hormones of circulatory importance, especially in essential hypertension and in manifest renal disease

RESPONSE OF RENAL CIRCULATION TO PATHOLOGIC DISTURBANCE

The kidney participates in vasomotor reflexes which act to preserve brain and heart blood pressure. Thus congestive cardiac failure, orthostatic hypotension, inhaled carbon dioxide, pain (the cold pressor test), fright, anxiety, unconscious psychic conflict, surgical operation, trauma (the renal crush syndrome), hemorrhage, and shock, all dramatically reduce renal blood flow Epinephrine and neural vasoconstriction are responsible (Smith, Trueta et al; Bull). In fainting (vasovagal syndrome), the kidney joins in the systemic vasodilatation.

Nephrectomy, after transient effects, leaves the remaining normal kidney hypertrophied, particularly in patients under the age of 30, with function and blood flow rising to reach about three-fourths of the normal for two kidneys (Smith)

In *pyelonephritis*, although blood flow per unit functioning kidney is near normal, the actual flow rate is reduced Filtration falls less

By contrast, *chronic glomerulonephritis* shows a fall in filtration fraction with plasma flow less affected per unit functioning tissue.

Oliver has well described the anatomic changes, especially the development of abnormal nonfiltering glomeruli, in Bright's disease.

The incidence of hypertension in *pyelonephritis* and *glomerulonephritis* does not correlate with a change in renal circulation. The elevated blood pressure does not appear to be compensatory in fact, increasing renal circulation, but it may be argued that, without hypertension, flow would have been reduced

In *hydronephrosis*, renal flow falls but is not abolished

Toxemia of pregnancy lowers filtration rate moderately, with renal blood flow staying normal or rising slightly, reduction in filtration fraction is therefore the prominent finding

In *cardiac decompensation*, renal blood flow is markedly reduced, perhaps halved, filtration falling somewhat less. The relative importance of elevated venous pressure, hypoxia (the arteriovenous oxygen difference is increased), and neurohumoral and humoral vasoconstriction is not yet elucidated The current view of the role of the kidney in cardiac failure is that it retains salt and water because of excess of circulating hormone (*aldosterone*), not because of its lowered circulation

Renal ischemia of severe degree develops in induced hypothermia When long maintained, ischemia causes parenchymal damage

The role of the kidney in *essential hypertension* continues to be a mystery. Restriction of blood flow by partial clamping of the renal arteries (many other related methods have been described) in animals causes a *chronic* hypertension, probably involving angiotensinase-angiotensin (renin-angiotonin) production at least initially The simple analogue in man is not as rare as had been supposed. X-ray renal arteriography reveals cases previously overlooked, as when a tumor partially occludes a renal artery (Smith).

VEM is produced by the kidneys in this type of hypertension, but its influence is soon neutralized by a concomitant rise in VDM, and these substances are not the cause of the high blood pressure (Wakerlin).

In renal and in many cases of essential hypertension, there is no fall in blood flow through the kidneys Of course, immediately after the constriction of a renal artery by a *Goldblatt clamp*, there is a fall, but the arteriolar vasodilatation of autoregulation and the rise in systemic blood pressure soon provide normal renal blood flow and function More commonly, in *essential hypertension*, both plasma flow and the effective secretory capacity of the kidney decline, the latter disproportionately less, so that a functional ischemia results

Renoprival hypertension develops in nephrectomized dogs treated to prevent uremia. Again, the relation of this phenomenon to the many other observations it has stimulated and to essential hypertension itself is obscure If the ureters are transplanted into the peritoneum so that the kidneys secrete without actual excretion, hypertension is prevented It would appear that the normal kidney, irrespective of innervation and excretion, has a hypertension-reducing function (Kolff) The kidney very likely plays an essential role in the development of what, in the present state of ignorance, is called essential hypertension It is also probable that some homeostatic mechanism related to kidney circulation is involved Whether ischemia, lowered capillary pressure, reduced pulsation, or some other intrarenal hemodynamic factor is the primary disturbance to which the elevation of systemic blood pressure is the homeostatic response, cannot yet be told.

Clotting: a theory of the hemostatic process in relation to thromboembolic phenomena

MARIO STEFANINI AND FRANCO GOBBI

The hemostatic process is primarily intended to protect the body against harmful blood loss. In *lower species*, this is achieved primarily by the simple mechanisms of vasoconstriction and mechanical plugging of blood vessels by "clumps" of platelets or of analogous elements. In *mammalians*, a higher intravascular pressure brings about the necessity for additional mechanisms (such as coagulation of blood) to assure firm closure of the injured vessel. The hemostatic mechanism becomes, then, of ever-increasing complexity.

HEMOSTASIS

The Phases of the Hemostatic Process. The phases of hemostasis are perhaps understood best by considering the sequence of events after lesion of a vessel (Diagram 2-1). In man and, very likely, in all mammals, hemorrhage most often follows injury to a metarteriole. An analytic reconstruction of the response of the metarteriole to injury has become possible through observation of directly visualized vessels in the vascular bed of the nail in man, and in the hamster pouch and the ear chamber of the rabbit.

Injury to the vessel is followed by immediate *vasoconstriction*, limited to the area of injury. Although it is of short duration, its hemostatic effectiveness may still be significant, since the vasoconstriction affects the vessel *above* the area of the lesion. It also causes a rearrangement of the formed elements of the blood within the vascular bed. Thus, platelets (normally traveling at the center of the blood stream) become peripheral, coming thereby in contact with the area of vascular lesion. The initial vasoconstriction following injury is currently held to be the result of an "axon reflex." Alternative explanations may be equally valid.

DIAGRAM 2-1 HEMOSTASIS FOLLOWING VASCULAR INJURY: A MULTIPHASIC PROCESS

1. *Local vasoconstriction* ⟶ platelets to periphery of blood stream
2. *Agglutination of platelets* ⟶
   - formation of *white thrombus*
   - generalized vasoconstriction (? indolamines liberated)
   - liberation of thromboplastic factors
3. *Coagulation of blood* ⟶
   - formation of a lipoprotein thromboplastic substance
   - formation of prothrombin-converting enzyme (prothrombinase)
   - formation of fibrin → *red thrombus*
4. *Retraction of blood clot*
5. *Lysis (?) of clot*

Thus, the lesion of the intima might liberate vasoconstrictor substances which are present in many tissues into the *area of injury*.

Interruption of the continuity of the vascular wall has a number of disturbing effects. It creates a "rough surface" whose electric charge is no longer uniform. Also, it may free tissue thromboplastic substances. Both these mechanisms produce precipitation or agglutination of platelets at the site of vascular injury. This institutes the second step in the hemostatic process, i.e., the *formation of a "white thrombus"* The white thrombus has a very *important role in hemostasis*. It may represent a self-sufficient hemostatic mechanism in capillary vessels. In larger vessels, it supplies an irregular surface, which is known to enhance blood clotting; even more important, it supplies the platelet factor which is needed for the initiation and the rapid progression of the early stages of the blood coagulation process. The formation of a white thrombus initiates also a rapid series of events, the most significant being diffuse vasoconstriction and blood coagulation. *Persistent, generalized vasoconstriction* follows vascular injury, especially if there is significant blood loss. It is generally held, although not clearly proved, that vasoconstriction is due to liberation of active substances from the agglutinated and, then, lysed platelets. Platelets seem, in fact, to contain a number of agents with local as well as general vasoconstrictor effect, such as *serotonin* (5-hydroxytryptamine), and, possibly, many other indolamines and catecholamines. It is, of course, possible that generalized vasoconstriction may be unrelated to the activity of platelets and rather due to the chemicals which may become liberated in the course of hemorrhage, especially if complicated by shock. Shortly after platelets have agglutinated at the site of injury, a series of mechanisms (see below) lead to the formation of a *"red thrombus,"* or *clot*. After it has become formed, *the clot retracts*, a phenomenon which is spectacular in vitro, but probably of little significance in vivo. It has been said that the retraction of the clot approaches the walls of the injured vessel and, thereby, facilitates *the formation of a permanent clot*. A consideration of the physical forces involved in such a process makes this hypothesis untenable. It is, however, true that, from a dynamic viewpoint, a retracted clot is probably a better "hemostatic plug" because of its greater strength. Also, it represents a better vehicle for the invasion of connective tissue which brings about the formation of the final, organized clot.

The preceding paragraphs emphasize the basic importance of platelets in the hemostatic process, where they act as intact bodies and as source of chemical factors. Phenomena such as agglutination at the site of injury and retraction of the clot require the integrity of the platelet body. On the other hand, vasoconstriction and blood coagulation require primarily "chemical" platelet factors. Among these, some are intimate constituents and some are simply carried by platelets within the circulation (*Table 2-8*). Factors which are carried (absorbed) by platelets are carotenoids, other pigments, epinephrine, serotonin, and many vasoconstricting agents. Also carried by the giant lipoprotein molecule of the platelet are many

TABLE 2-8 CONSTITUENTS OF HUMAN PLATELETS

Intimate components	*Constituents absorbed on platelets*
1 Factor II	1 Many coagulation factors
2 Thromboplastic factor (III)	*a* Fibrinogen
3 Antiheparin factor (IV)	*b* Labile factor (so-called platelet factor I)
4 Pigments (carotenoids)	*c* AHG
5 Enzymes	Etc
a Dehydrogenases	2 Antifibrinolysin, other factors of the fibrinolytic system
b Oxidases	3 Serotonin, indolamines, catecholamines, epinephrine, etc
c Esterases	4 Histamine(?) *
d Phosphatases	
e Arginase	
f Peroxidases	
g Glutamic oxaloacetic acid transaminase, etc	

* Certainly found in rabbit *platelets*

Clotting: a theory of the hemostatic process in relation to thromboembolic phenomena

MARIO STEFANINI AND FRANCO GOBBI

The hemostatic process is primarily intended to protect the body against harmful blood loss. In *lower species*, this is achieved primarily by the simple mechanisms of vasoconstriction and mechanical plugging of blood vessels by "clumps" of platelets or of analogous elements. In *mammalians*, a higher intravascular pressure brings about the necessity for additional mechanisms (such as coagulation of blood) to assure firm closure of the injured vessel. The hemostatic mechanism becomes, then, of ever-increasing complexity.

HEMOSTASIS

The Phases of the Hemostatic Process. The phases of hemostasis are perhaps understood best by considering the sequence of events after lesion of a vessel (Diagram 2-1). In man and, very likely, in all mammals, hemorrhage most often follows injury to a metarteriole. An analytic reconstruction of the response of the metarteriole to injury has become possible through observation of directly visualized vessels in the vascular bed of the nail in man, and in the hamster pouch and the ear chamber of the rabbit.

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- formation of fibrin → *red thrombus*

4 *Retraction of blood clot*

5 *Lysis (?) of clot*

analyzes the almost endless number of theories of the blood-coagulation mechanism which are offered by various investigators. The hypothesis presented here (Fig. 2-89) reflects primarily the personal experience of the authors.

The central step of the coagulation process is the formation of an enzyme converting prothrombin to thrombin. The enzyme is an easily sedimentable product, probably proteolytic, which originates from the interaction of many coagulation factors, whether from platelets or plasma. Its formation *may proceed through several steps of fairly long duration,* possibly taking up most of the time during which the blood collected in a test tube remains fluid. A tentative reconstruction of this phase is as follows: antihemophilic globulin and platelet thromboplastic factor intereact first in the presence of *accelerators (PTC, PTA, Hageman's factor)* to yield an intermediate product, equivalent to tissue thromboplastin. The thromboplastic product reacts then with the stable *factor*[a] to form a second intermediate product. This, in turn, reacts with the labile *factor* to form blood *thromboplastin* or *prothrombinase.* No proper place can be found at this time for the newly described Prower and Stuart factors, because of the vagueness of their properties. Infinite variations to this hypothesis are possible and many have been presented. Diagram 2-2 portrays one which has the support of solid experimental findings. It is suggested that the first phase of the formation of blood thromboplastin is *the interaction of AHG, PTC, Hageman's, Stuart's and other factors of the same group to form a first, nonsedimentable complex. This, in turn, reacts with platelets or their by-products to form a sedimentable product.* The reaction of the latter with the labile factor would bring about the formation of blood thromboplastin. This second scheme has no place for the stable factor and denies any role of this agent in the formation of thromboplastin. Nevertheless, patients recognized as having stable-factor deficiency exhibit a characteristically prolonged prothrombin time of plasma, which indicates a deficiency in the late stages of thromboplastin formation. The interpretation of the further stages of the coagulation process are not contested. *Prothrombinase probably "liberates" thrombin from the precursor prothrombin, as the thrombin molecule is smaller than that of prothrombin.* In a third phase of the clotting process, *fibrinogen is converted to fibrin by the enzyme thrombin.* It is generally admitted that since fibrinogen and fibrin possess the same antigenic properties and the same chemical composition, the conversion of fibrinogen to fibrin may consist in an internal mo-

[a] The stable factor may include more than one entity.

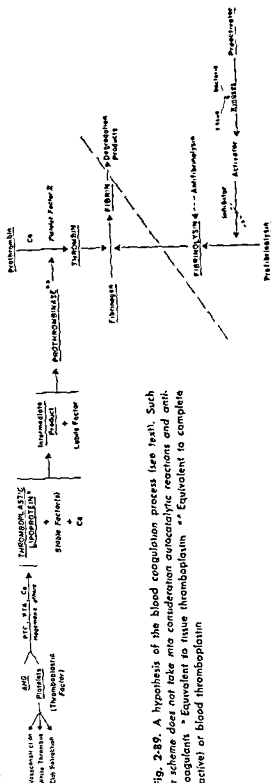


Fig. 2-89. A hypothesis of the blood coagulation process (see text). Such a scheme does not take into consideration autocatalytic reactions and anticoagulants. * Equivalent to tissue thromboplastin. ** Equivalent to complete (active) or blood thromboplastin.

TABLE 2-9. FACTORS PARTICIPATING IN THE PROCESS OF BLOOD COAGULATION AND THEIR SOURCE *

Platelets †	*Plasma*	*Serum* §
A. Platelet factor II	*A* Agents favoring blood coagulation	
B. Platelet thromboplastic factor (factor III)	1 Antihemophilic globulin (AHG)	
	2. Plasma thromboplastin component (PTC)	1. PTC
C Platelet antiheparin factor (factor IV)	3 Plasma thromboplastin antecedent (PTA)	2 PTA
	4 Hageman's factor	
	5 Stuart's factor	
	6 Prower's factor	
	7 Prothrombin	
	8 Labile factor	3 Serum accelerator
	9 Stable factor	4 "Activated"(?) stable factor
	10 Fibrinogen	
	11 Calcium	5 Calcium
		6 Thrombin
		7 Metathrombin
	B Agents opposing blood clotting or destroying the formed clot ‡	
	12. Antithromboplastins	8 Antithromboplastins
	13 Antithrombins	9. Antithrombins
	14 Albumin X (heparin cofactor)	10 Albumin X
	15 Profibrinolysin	11 Profibrinolysin
	16 Antifibrinolysin	12 Antifibrinolysin
	17 Antifibrinolysokinase	13 Antifibrinolysokinase

* See text for explanation

† Many of the factors active in the formation of thrombin or part of the fibrinolytic system and fibrinogen itself are absorbed to platelets.

‡ Other anticoagulants have been postulated in addition to those here listed, including inhibitors of labile and stable factors, of prothrombin etc

§ Serum also contains variable, usually small amounts of AHG and prothrombin, depending on the degree of their utilization during the process of blood coagulation

factors known to be involved in the process of blood coagulation, including labile factor,[1] fibrinogen, prothrombin, stable factor, antihemophilic globulin (AHG), and antifibrinolysin. Among the intimate constituents of platelets are *many enzymes*, whose role in the hemostatic process is unfortunately unknown [2], *platelet factor II*, a poorly characterized agent which is said to accelerate the conversion of fibrinogen to fibrin, the *thromboplastic factor*, a lipoid or lipoprotein known to be indispensable for the formation of blood thromboplastin, an *antiheparin factor*, which shares many properties with the thromboplastic factor.

COAGULATION OF BLOOD

Factors needed for blood coagulation are found in platelets, plasma, and serum (Table 2-9). The platelet factors have been briefly mentioned in the previous paragraph Many of the coagulation factors found in plasma are also found in serum, where their concentration is in inverse relationship to the extent of their utilization during clotting. Also, serum contains agents which develop through either activation of less active plasma precursors or neutralization of active factors during the process of blood coagulation As for the platelet factors, no attempt will be made here to describe in detail the characteristics and properties of the coagulant agents of plasma and serum, they will only be briefly mentioned. *Prothrombin* and *fibrinogen* act primarily as substrates of the final phases of coagulation *Calcium* is essential in all phases of the coagulation process Other factors take part in a number of reactions leading to the formation of intermediate enzymatic products acting on prothrombin or on fibrinogen Without attempting to discuss critically a subject which is still most confused, it appears that the following substances should be considered as primary coagulation factors *antihemophilic globulin, plasma thromboplastic component (PTC), plasma thromboplastic antecedent (PTA), Hageman's factor, Stuart's factor, labile factor, and stable factor.*

The complexity of the relationship of the various clotting factors becomes clear when one

[1] The platelet factor I, previously thought to be a *primary* platelet factor, is a labile factor absorbed from plasma.

[2] They include dehydrogenases, oxidases, esterases, phosphatases, arginase, peroxidases, and glutamic oxaloacetic transaminase.

hibitor of the clotting process in the presence of a globulin fraction (*albumin X*). It may play a physiologic role, since traces of this substance are found in the circulation. A similar role may be postulated for some acid polysaccharides, also found in plasma. An additional mechanism of inhibition of blood clotting is tied to phenomena of proteolysis Fibrinolysis, for instance, is followed, among other effects, by the liberation from fibrin of a polypeptide, similar to heparin, which acts as an anticoagulant. Such a mechanism, however, is likely to be operating only in pathologic conditions.

FIBRINOLYSIS AND PROTEOLYSIS IN HEMOSTASIS AND BLOOD COAGULATION

Proteolysis may play an important role in the mechanism of blood clotting. At least two coagulation reactions may be *proteolytic in* nature. (1) the conversion of prothrombin to thrombin by *prothrombinase*, (2) the formation of fibrin from fibrinogen by *thrombin* Other proteolytic phenomena may contribute to the final destruction of the clot under normal conditions Exaggeration of these mechanisms may be followed by hemostatic breakdown in pathologic states.

A specific system is found in the blood able to destroy the fibrin clot and to digest circulating fibrinogen. In normal individuals, this system is inactive, at least as indicated by available techniques. The complexity of the fibrinolytic system (Fig 2-89) compares well with the complexity of the blood coagulation itself An inactive precursor (*profibrinolysin*) is converted to fibrinolysin by an activating mechanism This consists of a plasma proactivator, which is converted to activator by kinases These kinases may be of bacterial or of tissue * origin There are two inhibitors, one for the proactivator and the other for the active fibrinolysin (antifibrinolysin) The nature of the activating agent is apparently important in determining the final "action" of the enzyme Thus, *fibrinolysin activated by bacterial kinases* is rather indiscriminate and destroys not only fibrin and fibrinogen but also other coagulation factors, particularly labile factor, PTC, and AHG The *fibrinolysin activated by tissue kinases* (such as urokinase) is more specific and digests exclusively fibrinogen and fibrin.

This brief résumé emphasizes the delicate balance upon which the process of blood coagulation is based, made up as it is of carefully matched opposing forces. The process, however, is well "buffered," *since only considerable* imbalance may upset the equilibrium and cause either hemorrhage or intravascular clotting Many clinical observations indicate that failure of one of the hemostatic mechanisms is compensated readily by the activity of others *Isolated* deficiencies of vasoconstriction, platelet agglutination, formation of the red thrombus (blood clotting) are not necessarily followed by significant clinical bleeding This aspect of hemostasis is even more evident during blood coagulation Isolated deficiency of most clotting factors must be very severe before bleeding ensues, probably because of the compensatory effects of the autocatalytic-like reaction of blood coagulation.

THE BASIC NATURE OF THROMBOEMBOLISM

Even in normal conditions, there is continuous clotting within the vessels in vivo Evidence for this statement is that a thin coat of fibrin may be found to line the vascular intima as well as the platelets and that the turnover of the clotting factors is rapid as compared to that of other plasma proteins Such processes may become exaggerated under pathologic conditions.

The pathogenesis of thromboembolism is now clarified by the previously described mechanism of clot formation This follows the agglutination of platelets at the site of a vascular injury The clot extends along the wall of the vessel, probably because of the presence of thrombin on its surface, which agglutinates platelets and may, thus, perpetuate the process of intravascular clotting This mechanism supplies an adequate "hemostatic plug." Without proper balancing, however, it could cause extensive, dangerous intravascular clotting. The prevention of excessive clotting depends only in part on the activity of circulating anticoagulants There are many physical factors of equal importance Thus, the integrity of the vascular wall and the maintenance of a steady blood flow prevent undue contact between *vascular wall* and platelets The exaggeration of clot-

* These kinases are found in many tissues and in many secretions (saliva, urine, milk, etc.)

DIAGRAM 2-2. AN ALTERNATE EXPLANATION OF THE FORMATION OF PROTHROMBINASE (BLOOD THROMBOPLASTIN)

Phase I: AHG + PTC + Stuart factors group + Hageman's factor, etc → product I
Phase II: Product I + platelets → product II (sedimentable)
Phase III. Product II + labile factor → prothrombinase (sedimentable)
↓
Prothrombin → thrombin

lecular rearrangement during which the large molecules of fibrinogen undergo a process of tridimensional polymerization As retraction proceeds, there is stretching of the clot, as longitudinal fibers become drawn together (Fig 2-90).

The theory does not take into consideration anticoagulants or fibrinolytic mechanisms, to be discussed later. More important, it does not emphasize the importance of phenomena of autocatalysis in the coagulation of blood The presence of anticoagulants, the "washing" effect of bleeding, the self-limiting intensity and duration of all chemical reactions, would tend to cause progressive deceleration and, finally, arrest of the blood-clotting process. Formation of blood thromboplastin, however, proceeds at increasing speed, because of phenomena of acceleration during blood coagulation These phenomena are of an autocatalytic-like type and depend almost entirely on the activity of a final product of the reaction, *thrombin*, which, in turn, catalyzes its own formation Autocatalytic-like processes during blood coagulation are summarized in Diagram 2-3

Autocatalytic reactions represent a potential danger to the welfare of the human body, since, unless checked, they would unavoidably be followed by total intravascular clotting There are, however, a number of mechanisms limiting the intensity and progression of the autocatalytic-like processes Some are entirely nonspecific, such as the effect of absorption of clotting agents, particularly thrombin, by plasma proteins. Another nonspecific inhibitory mechanism is the *red clot itself*, which absorbs thrombin (and possibly other factors) and releases them slowly later, as clot retraction takes place. At such time, they may be disposed of more easily by the specific anticoagulant agents There are also anticoagulants whose activity may be specific, although poorly understood, such as *sphyngosine* (which is found in plasma) and *phosphotydilserine* (which is found in platelets). Finally, one or more inhibitors are found against each known primary coagulation factor. Other inhibitors regulate the extent and speed of each phase of the clotting process One of the best identified specific anticoagulants is *antithrombin*. In the presence of antithrombin, *thrombin* is converted reversibly to a derivative, *metathrombin*, which is found in the serum. *Heparin* is an active and potent in-

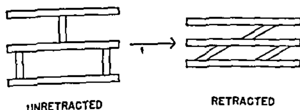
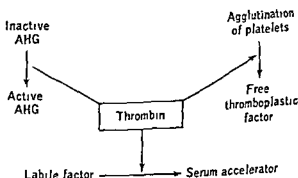


Fig. 2-90. Graphic representation of clot retraction In the unretracted clot, fibrin fibers are arranged as a regular net with platelet present in clusters at the point of junctions. In the retracted clot, fibrin strands keep the same relationship to each other but the longitudinal fibers appear drawn together (Courtesy of Dr R. Greene and Dr. E. Lozner, Syracuse, New York.)

DIAGRAM 2-3 MECHANISMS OF AUTOCATALYSIS IN BLOOD COAGULATION FOLLOWING FORMATION OF THROMBIN *



* Formation of small amounts of thrombin is followed by (1) activation of antihemophilic globulin (AHG) from an inert precursor; (2) further agglutination of platelets and subsequent release of more platelet thromboplastic factor, (3) conversion of labile factor into serum accelerator, a more powerful activator of the formation of blood thromboplastin.

SUMMARY OF LABORATORY TESTS USED FOR DETECTION OF THROMBOTIC TENDENCY

1 Physical properties of blood.
   a Viscosity
   b Electrical resistance
   c Sedimentation rate
   (d Thromboelastography)
2 Clotting time of blood:
   a. Clotting time of whole blood at various temperatures { glass test tubes; silicone test tubes (other nonwettable surfaces) }
   b Clotting time of recalcified plasma
   c "Sensitized" clotting time (heparin), whole blood and plasma
3 Platelets:
   a. Number
   b Agglutinability
   c Adhesiveness
   d Clot retraction (speed and extent)
4 Analytical study of single phases of the clotting process:
   a Prothrombin consumption
   b Thromboplastin generation
   c Thrombin generation
5 Analytical study of single factors of the clotting process
   a Prothrombin, activity and concentration
   b. Stable factor, activity
   c. Labile factor, activity
   d Antithrombin activity
   e Fibrinogen
   f Detection of fibrinogen polymerization products fibrinogen B
6 Fibrinolysis and proteolysis
   a Proteolytic activity, fibrinolytic * activity of plasma and serum (by various methods)
   b Activity of profibrinolysis (activation by bacterial or tissue kinases)
   c Antifibrinolytic activity

* At present three methods are considered adequate for this study (1) lysis of clotted euglobulin (contains no inhibitors), (2) thromboelastography; (3) degradation of synthetic substrates (also applied to studies of proteolysis)

The significance of "*hypercoagulability*" is doubtful A large number of tests has been described to identify a "hypercoagulability state" A review of the literature shows, however, that no test gives thus far adequate indication that the coagulation of blood is faster or that the yield of coagulation products is higher than normal in the blood of patients with phlebothrombosis or thrombophlebitis, or in those about to develop them The few and doubtful changes reported from time to time have usually been found *after* rather than *prior to* the occurrence of intravascular clotting, they are likely to be the consequence rather than the cause of intravenous clotting

The authors have had the opportunity of studying in the past many cases of so-called "familial thrombophilia" In one such family, the condition is of such severity that simple venipuncture is followed by extensive phlebitis, and two members of this family have died of extensive venous thrombosis following surgery Even in such an extreme state, batteries of tests have failed to document "hypercoagulability" of the venous blood The only clue has come from a modification of the [illegible] anomalies, whether in platelets, plasma, or serum Members of the "thrombophilic" family show no significant anomaly of thromboplastin generation If a system is set up, however, consisting of normal platelets and plasma and of the patient's serum, the generation of thromboplastin takes place more rapidly Since the final yield of thromboplastin is unmodified, the result suggests the presence of an active coagulant factor in the patient's serum (Fig 2-92) Extension of this work to a series of patients with acute thrombophlebitis, however, has given uniformly negative results It should be noted, in any case, that most of the tests proposed attempt to detect evidence of "increased" levels of coagulation factors or of "acceleration" of the clotting process The authors' studies on the pathogenesis of the extensive arterial intravascular clotting which occurs in amniotic embolism, separation

ting processes or the failure of any anticoagulant mechanism may bring about intravascular clotting.

Since Aschoff, causes for intravascular clotting have been held to be (1) injury of the intima of the vascular wall; (2) slow circulatory flow; (3) a poorly defined entity known as "hypercoagulability"; or a combination of these factors. *It should be emphasized that the* respective role of these etiologic factors is not firmly established by either experimental work or clinical studies. They are operative in both venous and arterial thrombosis, although their relative importance varies a great deal from one to the other (Fig. 2-91).

Venous Thrombosis. A *reduction in speed of the circulatory flow* is obviously an important mechanism in thrombosis of veins This may occur, because of many factors, even when the vessels are entirely normal. The backward pulsation of veins (venous pulse) and the weakness of the musculature at points around the valves contribute to reduce blood flow in the larger vessels Angulation and kinking of veins through anatomic position, or external pressure by prostheses, are also important.

Blood stasis alone does not of necessity induce the formation of a thrombus, as seen in human disease. Thus, if one injects fresh serum or purified thrombin into an isolated but intact vein, a ball clot is formed because of the immediate effect of the thrombin on fibrinogen and the formation of a clot of fibrin. This clot eventually assumes various shapes depending on local conditions, but does not adhere to the wall of the vessel if this is intact; no true thrombus will develop. Results are essentially similar if thrombin is injected above a point of ligature of a venous vessel to avoid *lesion to the vascular wall in the area of experi*ment by the needle introducing the clotting materials On the other hand, scarification of the intima of a similarly prepared vessel is immediately followed by the formation of a thrombus, which progressively extends to fill most of the vein The last consideration indicates the importance of *lesions of the vascular wall* in the pathogenesis of venous thrombosis Causes of injury to the intima may be trauma, inflammatory or necrotizing changes of the vascular wall, phlebitis, etc.

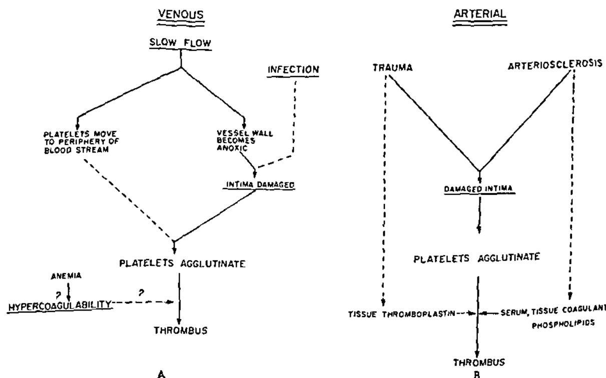


Fig. 2-91. Pathogenetic mechanisms: venous and arterial thrombosis. A In venous thrombosis slow circulation may be the most significant factor, leading, among other effects, to lesions of the intima through hypoxia; local infection, trauma, hypercoagulability (anemia) may contribute. B. In arterial thrombosis, changes of the intima due to arteriosclerosis or, more rarely, to other disease processes are most important. Local hypercoagulability may also be significant, and produced by tissue destruction and changes in the chemical structure of the vessel wall.

sel.[5] Thus, *lesion of the intima* is a pathogenetic factor of obvious importance. On the other hand, *stasis* is not likely to play any significant role unless exceptional circumstances exist, i.e., the presence of aneurysms causing eddying of the circulation *Hypercoagulability* is a disputed factor. It is not known whether changes found in the venous blood express faithfully those of the arterial blood In any case, no significant correlation has ever been found between arterial thrombosis and biochemical changes in the venous blood suggesting "hypercoagulability" The rare occurrence of coronary thrombosis in hemophiliac patients indicates, in fact, that even extreme hypocoagulability of the blood is not a guarantee against thrombotic occlusion. Recent biochemical studies, however, indicate the possibility that the normal chemical structure of the arterial wall might play a role in arterial thrombosis An extract of aorta exhibits proteolytic activity and high content of profibrinolysin, and also contains thromboplastic material When, however, the concentration of clotting and lytic agents in the various layers of the vessel is analyzed, the thromboplastic activity is highest in the intima, the fibrinolytic activity, highest in the adventitia, low in the intima and media Thus, release of thromboplastic material which follows injury of the intima may facilitate blood clotting at the site of the lesion Another local condition presumably favoring hypercoagulability and blood clotting seems related to the changes in chemical structure which are found in arteriosclerotic vessels These, in turn, are associated with important modifications in the lipid composition of serum There is a great deal of information available on the nature of lesions of the arterial wall associated with thrombosis and their relationship to lipid metabolism and, in turn, on the relation of lipids to coagulation phenomena As already mentioned, coronary thrombosis usually occurs within vessels which are the seat of "arteriosclerotic" lesions, consisting in the subintimal deposition of lipoids The chemical nature of these lipoids is not entirely known, although cholesterol and phospholipids are certainly present Moreover, changes in the chemical structure of the arterial intima are correlated to a certain extent to chemical changes in the serum, which are constant in patients where arteriosclerosis of the coronary vessels is documented by clinical signs of occlusion. Cholesterol and lipoprotein fractions, designated as S_f 12-20, are elevated in the serum, especially in patients of the young age group, prior to as well as *following* coronary occlusion. It is not known whether phospholipids, neutral fats, and their derivatives are also increased, although it is generally held that hypercholesteremia is only a facet of a more extensive alteration of lipid metabolism, which almost always includes increase in phosphatide fractions With regard to the relationship of lipids to blood coagulation, it is well documented that *some phospholipids are essential for optimal coagulation of blood* Platelets contain numerous phospholipids, and platelet-free, lipid-free plasma does not clot unless phospholipids are added (such as tissue thromboplastin) Also, some phospholipids may substitute for platelets in the thromboplastin generation test.

An in vivo demonstration of the role of lipids in clotting is the shortening of the coagulation time following a fatty meal, although this finding is contradicted by some investigators Many phospholipids of basic nature and able to combine with calcium have clot-accelerating properties, and may substitute for platelets in a test of thromboplastin generation[6] Three phospholipids, in particular, which are found in platelets and in plasma [phosphotydilserine (PTSE), phosphotydilethanolamine (PTEA), and phosphotydilinositol (PTI)] have remarkable clotting activity It would be of great significance if such phospholipids could be identified among those present in arteriosclerotic plaques, and if serum of patients who develop arterial occlusion should show any increase in their content of clot-promoting phospholipids

It should be concluded (Fig 2-91) that *arteriosclerotic and other lesions of the vascular wall are primarily responsible for the occurrence of arterial thrombosis in general, and of coronary thrombosis in particular.* It is, however, true that many patients show arteriosclerotic plaques and other lesions of the coronary intima at autopsy who never develop coronary occlusion Thus, one should postulate

[5] Less frequently, subintimal hemorrhage may cause final occlusion of a diseased vessel This indicates the difficulty in deciding on a therapeutic approach

[6] As mentioned previously, other phospholipids (such as sphyngosine and sphyngomyelin) may have anticoagulant activity.

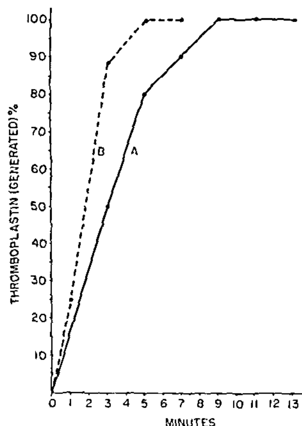


Fig. 2-92. *Thromboplastin generation test in thrombophilia. A, All reagents from normal blood, B, platelets and plasma from normal blood, serum from patient Note the more rapid generation of thromboplastin in B.*

of placenta with passage of thromboplastic material in the circulation, hemorrhagic shock, prostatic carcinoma, etc, indicates that it is accompanied by extensive defibrination and consumption of clotting factors

Thus, evidence for intravascular clotting or tendency to it should be sought, perhaps, not so much in the increased concentration of coagulation factors or in higher speed of elementary coagulation reactions but, rather, in the evidence of depletion of coagulation factors Phenomena of proteolysis are also important The study of the fibrinolytic system, for this reason, seems promising, although handicapped at present by significant technical difficulties. Finally, the role of "hypercoagulability" may be significant in a group of diseases in which there is an unexplained high incidence of thrombosis

This is most striking in carcinomas, especially those in the pancreas In these patients, thrombosis occurs usually in areas where there is no apparent direct effect of the malignant tissue. It may follow entrance into the blood stream of thromboplastic material. In generalized carcinomatosis this material may derive from breakdown of tumor tissue In the specific case of pancreatic carcinoma, trypsin may be the agent responsible for thrombosis Penetration of trypsin into the blood stream in this disease is suggested by the elevation of the serum antithrombin (antitrypsin) titer. At small doses, the enzyme facilitates clotting, while it increases lytic phenomena both directly and through activation of fibrinolysis at higher doses Intravascular clotting might then follow in each case, since proteolysis may indirectly produce thrombin from prothrombin and trypsin may also act as an equivalent of incomplete thromboplastin.

It would seem useful to attempt an interpretation of the sequence of events leading to intravenous thrombosis (Fig 2-91). All facts point to slow flow of blood and to injury of the intima as factors of primary importance. It is probable, however, that venous stasis is of greatest importance in *phlebothrombosis,* and injury to the intima in *thrombophlebitis,* a distinction which may be significant only in early stages of vascular occlusion. Slowing of the circulation produces rearrangement of platelets with respect to the vascular wall, and this facilitates agglutination of platelets. Also, the same factors producing slowing of blood flow may also induce *hypoxia,* leading to secondary lesions of the intimal wall, if they are not otherwise produced. Slowing of the circulation again facilitates the extension of the clot. As mentioned, this is in large measure because of high concentration of thrombin at the level of newly formed thrombin, initiating a sustained *autocatalytic* progression of the clot. This mechanism is reduced in importance by the washing effect of the circulating blood When this is minimized by a slow blood flow, the clot should and does extend more rapidly The role of hypercoagulability still remains uncertain.

Arterial Thrombosis. Arterial thrombosis offers entirely different pathogenetic problems Most of the discussion here refers specifically to the occlusion of coronary or of cerebral vessels, although the same considerations should apply to all arterial districts

It is likely that the pathogenetic factors involved in arterial thrombosis are similar to those described in venous thrombosis, although not in the same order of importance or sequence. Coronary or cerebral occlusion *is* most commonly due to thrombosis in the greatly narrowed lumen of a diseased ves-

injection of heparin is followed by the dissolution of chylomicrons, by the reduction of free and esterified cholesterol in plasma, and by lipolysis with release of fatty acids. The extent to which these metabolic activities of heparin account for its therapeutic effect in thromboembolism remains to be investigated.

A real challenge is presented by the possibility of lysing recent intravascular clots. The numerous attempts are hardly beyond the experimental stage (Diagram 2-4). Procedures which have been used in vivo include the administration of (1) shock-producing agents, particularly vaccines, (2) products with kinase activity obtained from bacteria and from tissues; (3) proteolytic enzymes, (4) a fibrinolytic fraction from human plasma; (5) a fibrinolytic agent obtained from aspergilli.

The intravenous administration of typhoid vaccine activates fibrinolysin. This technique has not been widely used because of the severity of the concomitant pyrogenic response. More extensively studied have been bacterial products with kinasic activity. The intravenous administration of purified filtrates from many streptococci and a few staphylococci produces a veritable hemostatic breakdown with rapid destruction of fibrinogen and other coagulation factors. It also induces a severe pyrogenic reaction because of a fraction that cannot be easily separated from the moiety with kinasic activity. Our chromatographic separation procedures, however, have yielded a product with good kinasic activity but little pyrogenic effect. Small intravenous doses, given to man over a period of hours, have induced intense fibrinolysis. Satisfying therapeutic results have been obtained in peripheral venous thrombosis and in deep venous thromboses (mesenteric, central retinal veins). Such methods have been followed by spectacular results, especially when the material had been injected immediately below the site of the thrombus. Unfortunately, too rapid breakdown of the clot has been observed, and pulmonary embolism has resulted in a few instances. A further development of this technique may be the use of kinases of tissue origin. Thus, the fibrinolytic activity developed from plasma after incubation with urokinase

from other sources, such as snake venoms. These are under investigation.

As mentioned, the clot-lysing activity of trypsin and chymotrypsin and, possibly, of other proteolytic enzymes involved in the mechanism of blood coagulation depends to a great extent on the dose used. *Small intravenous doses of trypsin have a coagulant effect. At higher doses, the enzyme causes destruction of fibrin and fibrinogen*, either through direct proteolysis or through activation of fibrinolysis. Also, trypsin has a very interesting, as yet unexplained, antiinflammatory effect. Intravenous and intramuscular trypsin has been used in the management of venous thrombosis and of coronary thrombosis. Results are mostly controversial. Finally, *preparations of purified human fibrinolysin (plasmin)* have been obtained in several laboratories. Such products are strongly effective in lysing intravascular clots. Difficulty in supply, however, makes it unlikely that human fibrinolysis will be used therapeutically in large scale.

The various modalities described here are probably effective in the management of *venous thrombosis*. Their use in *arterial thrombosis* is still problematic. Patients with severe coronary thrombosis and shock would seem a poor risk for the use of materials which are able to induce shock themselves. Many years of study have not revealed a fully successful technique of treating thromboembolism. The main reason is, perhaps, the lack of information on the intimate mechanism of the disease. One of the most discussed subjects in medicine, because of its interest to clinicians in many fields, thromboembolism is not less obscure today than half a century ago.

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the formation of a clearing factor from a plasma fraction

HEART, LUNG, PYLORUS (RAT)

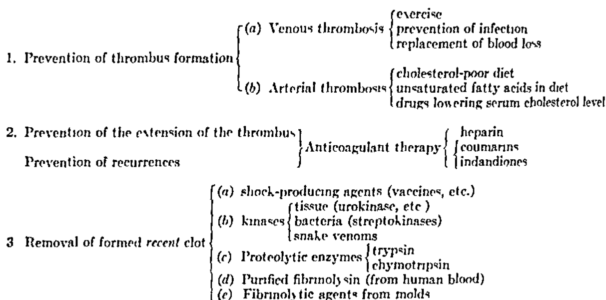
Plasma fraction IV-1 —(tissue factor / heparin)→ clearing factor

The clearing factor, in the presence of a second plasma protein, causes clearance of plasma.

Turbid lipoproteins (high S_f) —(clearing factor / coprotein)→ decreased turbidity (lower S_f)

Four major effects are observed: (1) decreased turbidity of lipemic plasma, (2) decrease in the ultracentrifugation flotation rates of low-density lipoproteins, (3) concomitant production of α-lipoprotein molecules, (4) reduction of cholesterol-bearing S_f 20 and S_f 20-100 lipoproteins.

DIAGRAM 2-4. A RATIONAL APPROACH TO THE TREATMENT OF THROMBOEMBOLISM



additional factors One of these might be represented by the concentration of clot-promoting factors of phospholipid nature in the serum, as well as in the arteriosclerotic plaques. This is admittedly little more than a speculation based on a few established facts.

A Rational Approach to the Management of Thromboembolisms (Diagram 2-4) Further insight into the pathogenesis of thromboembolism is given by some therapeutic considerations. Treatment of thromboembolism has three main goals: (1) to prevent the formation of a thrombus, (2) to prevent the extension of the thrombus, once it has formed, (3) to remove altogether the formed clot

Prevention of thrombus formation is still not entirely feasible, and it is still based on a few, empirical procedures An example is seen in the measures taken to prevent *venous thromboembolism* in postsurgical patients A few (frequent movements of body and limbs, deep breathing, pressure bandage of legs) are directed to accelerating return blood flow Antibiotics are given to control infection, an important predisposing factor of local and generalized thrombosis. Care is taken to replace fully any blood lost at operation to prevent the state of hypercoagulability which may follow anemia *A thrombus which is formed in an anemic patient has little surface and, therefore, is not able to adsorb thrombin and coagulation factors, a mechanism through which the body controls the autocatalytic reaction* The use of anticoagulants in small doses has been advocated but has failed to enter general use because of the potential danger of bleeding in the presence of open wound surfaces. The prevention of *arterial thrombosis* is based on its almost constant association with arteriosclerotic lesions of the vessels. Unfortunately, it is still dubious whether diets with poor intake of cholesterol, or those in which unsaturated fatty acids have been substituted for saturated ones, or the administration of drugs depressing the plasma cholesterol level, significantly reduces the occurrence of arterial thrombosis.

Anticoagulant therapy is primarily aimed at preventing the extension or the embolization of a thrombus which has already formed, and at preventing recurrence of thrombotic phenomena. Heparin and related drugs are true anticoagulants. They inhibit all phases of the clotting process in vivo and in vitro Their action, however, is primarily directed against thrombin, preventing the formation of fibrin and checking the autocatalytic reaction of blood clotting. *Coumarins* and *indandione* derivatives are "indirect anticoagulants" Through a mechanism of competitive inhibition, they depress the synthesis (by the mytochondria of the liver) of prothrombin, PTC, and stable factor(s)

Dicumarol and derivatives may also increase coronary flow They occasionally cause a drastic reduction in serum uric acid level, while the loss of weight of many patients receiving these drugs suggests their possible effect on lipid metabolism. This is certainly true of heparin In the presence of a tissue extract, heparin, in vitro, reduces the turbidity of lipemic plasma.[7] In vivo, the intravenous

[7] The following scheme summarizes the mechanism of the plasma-clearing effect of heparin In the first phase, a tissue factor and heparin engineer

injection of heparin is followed by the dissolution of chylomicrons, by the reduction of free and esterified cholesterol in plasma, and by lipolysis with release of fatty acids. The extent to which these metabolic activities of heparin account for its therapeutic effect in thromboembolism remains to be investigated

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As mentioned, the clot-lysing activity of trypsin and chymotrypsin and, possibly, of other proteolytic enzymes involved in the mechanism of blood coagulation depends to a great extent on the dose used Small intravenous doses of *trypsin* have a coagulant effect At higher doses, the enzyme causes destruction of fibrin and fibrinogen, either through direct proteolysis or through activation of fibrinolysis Also, trypsin has a very interesting, as yet unexplained, antiinflammatory effect Intravenous and intramuscular trypsin has been used in the management of venous thrombosis and of coronary thrombosis Results are mostly controversial. Finally, *preparations of purified human fibrinolysin (plasmin)* have been obtained in several laboratories Such products are strongly effective in lysing intravascular clots Difficulty in supply, however, makes it unlikely that human fibrinolysis will be used therapeutically in large scale

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HEART, LUNG, PYLORUS (RAT)

$$\text{Plasma fraction IV-1} \xrightarrow[\text{heparin}]{\text{tissue factor}} \text{clearing factor}$$

The clearing factor, in the presence of a second plasma protein, causes clearance of plasma.

$$\underset{(\text{high } S_f)}{\text{Turbid lipoproteins}} \xrightarrow[\text{coprotein}]{\text{clearing factor}} \underset{(\text{lower } S_f)}{\text{decreased turbidity}}$$

Four major effects are observed (1) decreased turbidity of lipemic plasma, (2) decrease in the ultracentrifugation flotation rates of low-density lipoproteins, (3) concomitant production of α-lipoprotein molecules, (4) reduction of cholesterol-bearing S_f 20 and S_f 20-100 lipoproteins

Cardiovascular effects of hormones, neurohormones, and vasoactive agents

Action of Hormones and Endogenous Agents

ERIC OGDEN

Cardiovascular Effects of Neurohormones and Hormones

WILHELM RAAB

ACTION OF HORMONES AND ENDOGENOUS AGENTS

A complete consideration of hormones and endogenous vasoactive agents as they act on the cardiovascular system calls for a three-part study of (1) those substances necessary for the basic activities of the components of the system, (2) those whose actions are so pronounced as to suggest that they are an important part of the regulatory mechanism, and (3) those whose actions appear to be minor, incidental, or poorly defined For each group, a complete discussion would cover its direct action on cells, tissues, and organs, and its various indirect actions on cardiovascular behavior With such an organization in mind, space can be conserved by the omission of much that would be obvious or repetitious, and much of a general nature that is fully discussed in works not dealing specifically with the cardiovascular system

This review will group endogenous vasoactive substances in three groups metabolites, hormones, and miscellaneous substances

METABOLITES

The metabolites, regardless of their individual actions at various sites, have in common the property of facilitating blood flow to their site of production.

Reactive Hyperemia. The general activity of the products of tissue metabolism is *to bring more blood to the part.* This is accomplished by local dilatation of blood vessels, notably arterioles and precapillary sphincters. Among such vasodilator influences may be mentioned lowered oxygen tension, raised carbon dioxide tension, raised hydrogen ion concentration, raised concentrations of phosphate, lactate, adenylic acid, urea, and histamine Experiments on reactive hyperemia suggest that the total effect of the accumulation of mixed metabolites may be more than additive (McDowall, 1956). An unknown vasodilator substance and a neurogenic mechanism have both been postulated without definitive evidence The universality of the reactive hyperemia concept is being called into question Among the metabolites cited, four call for special mention: carbon dioxide, lactate, urea, and histamine

Carbon Dioxide. This metabolite in physiologic concentrations dilates blood vessels by *local action on their musculature.* But when its tension in arterial blood rises, its medullary action tends to produce neurogenic vasoconstriction, which elevates arterial pressure and consequently facilitates the flow of blood to the vessels dilated at its site of production At all sites, the actions of raised carbon dioxide tension and of raised hydrogen ion concentration are difficult to disentangle precisely. In general, the distinction is of little practical significance,

since carbon dioxide tension and hydrogen ion concentration are intimately related in the buffering systems of both blood and cells and are both highly diffusible. The distinction, however, cannot be wholly ignored.

Lactate. In addition to its vasodilator action (Kurtz and Leake) and its well-known importance in muscle activity and general energy-liberating metabolic reactions, lactate deserves special mention as a preferential fuel for *cardiac contraction* (Lovatt Evans, 1936). The heart can derive its energy from the oxidation of lactate and can use it for glycogen formation.

Urea. The observation by Mines that urea (which occurs in concentrations of 2 per cent in elasmobranch blood) is essential to maintain the beat of elasmobranch hearts has been confirmed and extended. Urea in concentrations of *200 mg/100* ml improves the performance of the isolated frog heart, and in even lower concentrations, it increases the capacity of the dog heart to perform work at a given degree of dilatation. This action has not been clearly defined in human heart failure because of the difficulty of maintaining high blood urea levels in the absence of renal failure and of distinguishing between the increasing cardiac competence due to the diuretic effect of urea and its alleged effect on the heart.

Histamine. Estimates of the importance of histamine as a vasoactive substance have varied widely through the years. The similarity of the *shock state* induced by intravenous injection of histamine with that caused by extensive burns or traumatic tissue damage, taken together with the formation and absorption into the blood stream of histamine as a product of cell destruction, focused attention on histamine as a dilator of minute vessels. Careful studies of smaller doses of histamine suggest that *it commonly constricts small arteries and can thus* occasionally even elevate the blood pressure in the cat. Lewis's (1930) classical studies on the *triple response* of the skin to histamine establish it as a dilator acting directly on the minute vessels and by *nerve mediation (axon reflex)* upon somewhat larger vessels. In *these circumstances,* studied in detail mainly in the skin but validated by some experiments on *mucosae* by Weaver, the result to be expected would be the delivery of blood at high pressure to distended and possibly altered capillaries. This would favor the formation of extravascular fluid over its reabsorption. Such *extravasation of fluid,* if extensive subcutaneously (*edema*) into a traumatized region, into serous cavities, or to the outside through denuded skin areas, is likely to be an important factor in the hemoconcentration and hypovolemia of many instances of *shock.*

Histamine has been shown to be present notably in the venous blood from an active limb and is therefore thought by some to be an important contribution to the dilated state of vessels in active tissues (Anrep et al., 1935).

HORMONES

The endocrine system, whether considered in an individual species or on a *comparative* basis, appears to be organized to coordinate broad sweeps of physiologic behavior rather than to stimulate particular organs or organ systems. When considering the cardiovascular system, therefore, one finds that some hormones have marked actions, others, minor *ones according* to present understanding of the general functions of the particular hormone. This unifying concept of hormone action was perhaps first highlighted by Cannon's *emergency theory* for the adrenal medulla. One of the most striking examples is found in *prolactin,* which acts neither on epithelium, nor on skin epithelium, nor solely, on the *modified skin* epithelium of the mammary glands. It acts on epithelium only for the nutrition of the young, i.e., the hormonally prepared post-partum mammary gland or the crop gland with which the pigeon feeds its young.

This concept of physiologic, rather than anatomic, *organization* of hormone action greatly facilitates the study of the highly variable action of these substances on different structures.

Epinephrine-norepinephrine. This *mixture,* as secreted by the adrenal medulla, in anticipation or realization of the need for violent somatic activity, acts directly *on* the heart in several ways, having positive inotropic, chronotropic, dromotropic, and bathmotropic effects, and increasing the coronary flow.

Epinephrine has a positive *inotropic* effect, increasing t[illegible] stances anc[illegible] of the heart [illegible] *[illegible]ng.* These effects last longer than the chronotropic effect when observed in isolated hearts. In spite of the increase in heart rate, this substance also

increases the proportion of the cardiac cycle during which filling occurs most readily (Buckley, Sidky, and Ogden).

Most authors report *norepinephrine* to be without effect on the pulse rate or myocardial performance, but this is still open to some question (Hilton).

On the peripheral vascular system, the mixture seems to be dominantly a *venoconstrictor*, an *arteriolar constrictor* in the skin and renal areas, and an *arterial dilator* in vascular beds of striated and cardiac muscle; also it may possibly cause changes in the elasticity (rigidity) of the aorta. The question has been raised as to whether the stimulation of general cell metabolism may contribute to the dilator actions of these substances

The result of these effects is to either raise or lower the total peripheral resistance and simultaneously to shunt the blood flow to the organs of high metabolic rate (with the exception of the kidney). The accompanying constriction of the venous bed, together with the positive inotropic action on the heart, increases the cardiac output to such an extent that the blood pressure rises, even when the peripheral resistance is decreased. The exact pattern of the changes produced in systolic, diastolic, and pulse pressures is highly variable, depending upon the state of the organism (anesthesia, blood loss, etc.), the total dosage, the rate of injection or infusion, and probably other factors

Since the normal secretion commonly contains 20 per cent norepinephrine to 80 per cent epinephrine, the typical total effects are dominantly those of epinephrine somewhat modified by those of norepinephrine

Thus, a typical intravenous injection of the mixture causes *an increase of cardiac output* (ascribed to epinephrine) supported by *an increase in cardiac work capacity* (epinephrine and possibly norepinephrine) This increased cardiac output of itself would raise the blood pressure, an effect which is accentuated by norepinephrine, which raises the peripheral resistance, and antagonized by epinephrine, which lowers this resistance

The vascular changes described above with respect to their influence on cardiac output are so balanced that there is a *redistribution* not only of blood flow but also of the blood content of various tissues In this sense, the effect of the mixture can be compared to the "emptying of a reservoir." This mobilization of blood volume is accentuated markedly in some species by *contraction of the splenic musculature* In dogs, this mechanism can mobilize from storage a large fraction of the total blood volume, its magnitude and significance in man are certainly less and perhaps of no importance.

Experimentally, the mixture appears likely to effect a mass transfer of blood away from the heart and lungs. In naturally occurring emergencies, sympathetic excitation probably completes this transfer before the adrenal secretion arrives at its sites of action and thus provides the large amount of blood instantly necessary for sudden increases of cardiac output.

Posterior Pituitary Lobe Extracts. Posterior lobe extracts in general increase the activity of smooth muscle The fractionation into *oxytocin* and *vasopressin* (Pitressin P.D.) directed attention to the vasoconstrictor activity of the latter fraction *Vasopressin* in pharmacologic doses *constricts arterioles and venules* nonselectively and produces skin pallor, elevation of arterial pressure, and cardiac irregularity To make these effects evident, it is usually necessary to use blood levels higher than those produced by natural pituitary activity. Recent studies show an increase of peripheral blood flow during intravenous infusions (170 mμ/min) of vasopressin. This is thought to be mediated by the central nervous system.

Electrical excitation of the central end of the cut vagus in some species causes enough posterior lobe activity to raise the blood pressure as the result of liberation of vasopressin This is the so-called *"vagohypophyseal reflex" of Chang* (Sattler). Since the same substance (under the name antidiuretic hormone—ADH) is active in promoting water conservation in much smaller (and naturally occurring) concentrations, it is probable that this is to be thought of as an "antidrought" hormone whose physiologic vascular action in mammals is minor, perhaps vestigial, and not recognizable with any certainty in man unless it is used in unphysiologic doses (Van Dyke)

Adrenal Cortex. The influence of the secretions of the adrenal cortex on the cardiovascular system has long been suspected but is not yet well defined.

The hypotension and cold extremities characteristic of *Addison's disease* were subsequently observed clearly in adrenalectomized animals. When experimental hypertension came under intensive study, it was soon found that adrenalectomy counteracted existing hypertension or prevented its development Administration of whole cortical extract or desoxycorticosterone restored the blood pressure after adrenalectomy had lowered it in normal or hypertensive animals

More recent studies of the relationship of forced or restricted salt (NaCl) intake to blood pressure indicate that the above effects are inextricably connected with *mineral balance*. Apparently, the hypertensive organism is a water waster which eliminates water faster than sodium and thus tends to be in positive sodium balance This wastage of water represents a relative deficit in sodium elimination (Sapirstein) The mechanism by which this dehydration with relative sodium excess produces hypertension, if indeed it really does so, is unknown It is possible that other substances from the adrenal cortex may be vasoactive

Nasmyth reports that *hydrocortisone* dilates the coronary system and has negative inotropic and chronotropic effects depressing myocardial contraction and rate *Corticosterone* also depresses the heart but constricts the coronary vessels.

The most obvious cardiovascular actions of the adrenal cortex are referable to its mineral corticoids and should perhaps be thought of as incidental to the gland's organization for defense against salt shortages, which must have occurred commonly in our phylogenetic development, and possibly against salt excess associated on land with drought, and in our marine ancestors with failure to exclude the sea

Thyroid. Direct action of thyroid hormones on the cardiovascular system is unknown Increased heart rate, pulse pressure, and cardiac output, together with decreased arteriovenous oxygen difference, are characteristic of the hyperthyroid state. The simplest explanation is to be found in a generalized increase in tissue metabolism This leads to *increased cardiac output*, resulting in an increased pulse rate and pulse pressure. The high oxygen content of the mixed venous blood suggests that the skin receives an amount of blood determined not by its own metabolic activity but by its role in maintaining temperature equilibrium in the face of increased total body metabolism. The effect of environmental temperature on metabolic rate suggests that the vascular actions of the thyroid might all be secondary to its function as an adjustive mechanism for climatic changes.

The peripheral vascular manifestations of hypothyroidism are also almost certainly the results of the general metabolic decrease

The great susceptibility of the hyperthyroid heart to dilatation, atrial fibrillation, and other disorders has never been analyzed to the point of general agreement. Certainly, these hearts have more work to do constantly; they may be working less efficiently under the oxygen utilization drive of the hormone, and these two factors may predispose them to disease of other unrecognized etiology. More detailed studies have been made on the thyroprival heart, but here also the mechanism has not been elucidated

Renin. This protein (to date not purified) may be extracted from kidneys and is probably liberated into the blood stream whenever the stirring of intrarenal fluids is diminished by pulsations of the kidney (Ogden) Renin catalyzes the breakdown of a plasma *protein* (renin-substrate alpha-2 globulin, also called *hypertensinogen*), with the production of *angiotensin* (Braun Menendez and Page), which is a general arterial constrictor. An elevation of arterial pressure results Renin is liberated by the following experimental procedures, each of which is likely to diminish the expansile pulsation of the kidney, though this diminution has not been clearly shown experimentally (1) The *Goldblatt clamp*, designed to compress but not obliterate the renal artery This compression may be accomplished also by the application of a loose ligature, after which the kidney is encouraged to grow (either by using a growing animal or by removing the other kidney). (2) *Renal compression* by a perinephritic capsule. This may be produced by encasing the kidney in silk or cellophane, by coating it with collodion or latex, or by tying it tightly with a cord, making a figure of eight (3) Similar effects may be obtained by partial *nephrectomy* with the production of scarring

(4) The pulse pressure of the whole animal may be diminished by a moderate *hemorrhage*. This effect is probably reinforced by renal vasoconstriction, which hinders the diminished arterial pulsations from producing expansile pulsation of the organ.

Angiotensin. Angiotensin, the substance resulting from these changes in renal function, is a generalized vasoconstrictor. It has recently been studied in great detail and synthesized (Schwarz, Bumpus, and Page). The renin mechanism has been shown to be evoked promptly (in some experiments within 3 min—Ogden et al.) in response to very small hemorrhages (Collins and Hamilton) and may therefore have some significance as an adaptation to blood loss or trauma. Though this mechanism was first and most thoroughly investigated as a vascular control mechanism, more recent studies of its effects on renal function may eventually lead to a reevaluation of its basic physiologic significance.

Renin as a hypertensive agent is mainly of experimental significance. It may be concerned with acute hypertension, as in eclampsia, glomerulonephritis, blockage or kinking of a renal artery, or rapid pyelonephritis. The theoretic study of such cases is of considerable importance, but at present there is no certainty that the instances of surgical success from the removal of a kidney are due to the effect on the renin mechanism. Hypertension experimentally originating in one kidney may persist after the removal of that kidney, and since disease affecting one kidney is no evidence that the other is normal, the decision to remove a kidney is a surgical one to which the physiologist can at present contribute little.

Renoprival Hypertension. There is now little doubt that bilateral nephrectomy, however well the excretory function may be maintained artificially, leads to elevation of the blood pressure. Grollman has adduced many reasons for attributing this hypertension to the absence of a substance secreted by the normal kidney. His view has not been generally accepted, and the phenomenon may well be due to the same unknown mechanism which acts when hypertension is produced by loading with salt and desoxycorticosterone (see Adrenal Cortex, above). High-protein diet, alanine, pyruvate, and lactate appear to potentiate renoprival hypertension (Muirhead, Jones, and Stirman).

Insulin. Insulin, given with glucose in the heart-lung preparation, exerts a positive inotropic effect and counteracts the spontaneous progressive failure of these preparations (Bayliss, Mueller, and Starling). It seems likely that it promotes glycogen storage by the heart, and the cardiotonic effect may be related to the concomitant migration of potassium into the cells. Detailed investigations on this matter have not been found in the literature; moreover, there is no evidence that this is a significant regulatory mechanism. At present, it seems to be incidental to the general action of insulin on the cellular handling of glucose.

Gonads and Tropic Hormones. The cyclic influence of these substances on the vessels of the uterine mucosa during menstruation and gestation, though important, is incidental to the reproductive function and is more properly considered as such. This increased vascularity, which causes an increased pelvic blood flow, acts to some extent as an arteriovenous shunt and has been considered an important vasodynamic change in pregnancy. The same phenomenon, by raising pelvic venous pressure and further by causing congestion within the pelvic cage, tends to impair the return of blood through the pelvic veins and often precipitates the formation of *vulval or saphenous varices*. There is not enough evidence for the suggestion that the same chemical mechanism which causes vascular proliferation in the uterus may be responsible for a direct action on the veins of the lower extremity.

MISCELLANEOUS

Under this heading are grouped those substances which seem to deserve little mention and those whose vascular significance is not yet clear enough for other classification.

Serotonin. This substance, also known as 5-hydroxytryptamine, enteramine, thrombocytin, and thrombotonin, is found naturally in blood. It may be extracted from plasma as a complex of equimolecular parts of creatine, sulfuric acid, and 5-hydroxyindole base, and is a *powerful vasoconstrictor*. It has been known for 80 or more years that there was a vasoconstrictor power present in blood when it clots, and that this power does not appear when blood is prevented from clotting by sodium citrate.

One of the factors causing the appearance of

the vasoconstrictor serotonin in blood is *trauma to the blood*. The maximum release of serotonin from the platelets is within 15 min The small amount present in circulating blood due to the normal breakdown and destruction of platelets is below the threshold of detectable vasomotor activity, so it may be assumed that it plays little part in the maintenance of normal arteriolar tone.

After the injection of 10 to 200 µg of serotonin in the chloralosed cat, Reid found there is a depressor phase, or fall, in blood pressure followed by an increase in blood pressure lasting several minutes, then another depressor phase. He found this response whether or not the vagi were cut He attributed the first fall in blood pressure to *vasoconstriction in the pulmonary circulation* and to direct *vasoconstriction of the coronary vessels* The pressure phase was attributed to the direct vasoconstrictor action of the drug The pulmonary blood vessels seem to be especially sensitive to this substance

Page and McCubbin (1953) attributed the response to serotonin to four main actions of the drug (1) direct vasoconstriction, (2) a von-Bezold-like reflex, (3) transient ganglion blockage, (4) peripheral inhibition of neurogenic vasoconstrictors They believe that the relative prominence of these actions depends upon the dose of serotonin, species tested, and degree of preexisting neurogenic vasoconstriction When neurogenic vasoconstrictor tone is absent, no matter what the species, response to serotonin is pressor, when the neurogenic vasoconstriction is increased, the response is depressor

In small doses, serotonin produces a depressor response in normal dogs and man In larger doses, it produces pressor responses, therefore it seems that it takes only small doses to inhibit neurogenic tone This fact seems to go along with the assumption that serotonin is released from the platelets in large quantities at a time of trauma to enhance clotting and vasoconstriction Under normal conditions very small concentrations are present

Reid and Rand found that serotonin stimulated the adrenal medulla, but the difference in response as compared to that in an adrenalectomized animal was not appreciable Serotonin inhibits urinary flow, probably by its vasoconstrictor action

In summary, serotonin occurs naturally in blood in small quantities having little or no effect on the cardiovascular system. In larger amounts, as in trauma to the blood, serotonin is released from the platelets and acts as a vasoconstrictor. It has a direct stimulating effect on the adrenal medulla. Its vascular effects are much complicated by neurogenic adjustments The effects of serotonin vary from species to species

Proliferation of Blood Vessels. Proliferation of blood vessels in association with rapid growth, development, work hypertrophy, healing, and ischemia appears to have chemical causes but has not been investigated. In all these instances, two conditions appear to be necessary. First, blood vessels must be present for collateral development or proliferation to take place In the second place, there must be a "need," or ischemia, that is to say a blood supply which is insufficient for the activity. Whether the stimulus to proliferation is one of the known physiologically active principles, a combination of them, or a completely unknown mechanism, is not known

Kallikrein. This nondiffusible, noncrystalline, thermolabile depressor substance occurring in the urine, salivary, and pancreatic secretions has been known for many years Its significance is unknown, and little recent work has been done with it

Depressan. Depressan has been described as a heat-stable depressor extracted from boiled human urine.

VEM and VDM. A *vasoexcitor* and a *vasodepressor material* elaborated by the kidney and the liver, respectively, were studied intensively by Shorr and his colleagues More recent work casts serious doubt on their significance, largely because of the highly specialized technique used in the original studies

Sustained Pressor Principle of the Kidney. Studies on the renopressor mechanism discussed above have brought to light *several* pressors associated with the kidney, for none of which has any clearly defined *function* been assigned Of these, the "*sustained pressor principle*" (Helmer) seems to have stimulated more interest than the *others*

Acetylcholine. The vascular actions of acetylcholine are essentially those of the parasympathetic or, more precisely, *the cholinergic* autonomic nervous system, and a detailed discussion

(4) The pulse pressure of the whole animal may be diminished by a moderate *hemorrhage*. This effect is probably reinforced by renal vasoconstriction, which hinders the diminished arterial pulsations from producing expansile pulsation of the organ.

Angiotensin. Angiotensin, the substance resulting from these changes in renal function, is a generalized vasoconstrictor. It has recently been studied in great detail and synthesized (Schwarz, Bumpus, and Page). The renin mechanism has been shown to be evoked promptly (in some experiments within 3 min—Ogden et al.) in response to very small hemorrhages (Collins and Hamilton) and may therefore have some significance as an adaptation to blood loss or trauma. Though this mechanism was first and most thoroughly investigated as a vascular control mechanism, more recent studies of its effects on renal function may eventually lead to a reevaluation of its basic physiologic significance.

Renin as a hypertensive agent is mainly of experimental significance It may be concerned with acute hypertension, as in eclampsia, glomerulonephritis, blockage or kinking of a renal artery, or rapid pyelonephritis The theoretic study of such cases is of considerable importance, but at present there is no certainty that the instances of surgical success from the removal of a kidney are due to the effect on the renin mechanism. Hypertension experimentally originating in one kidney may persist after the removal of that kidney, and since disease affecting one kidney is no evidence that the other is normal, the decision to remove a kidney is a surgical one to which the physiologist can at present contribute little

Renoprival Hypertension. There is now little doubt that bilateral nephrectomy, however well the excretory function may be maintained artificially, leads to elevation of the blood pressure. Grollman has adduced many reasons for attributing this hypertension to the absence of a substance secreted by the normal kidney His view has not been generally accepted, and the phenomenon may well be due to the same unknown mechanism which acts when hypertension is produced by loading with salt and desoxycorticosterone (see Adrenal Cortex, above). High-protein diet, alanine, pyruvate, and lactate appear to potentiate renoprival hypertension (Muirhead, Jones, and Stirman).

Insulin. Insulin, given with glucose in the heart-lung preparation, exerts a positive inotropic effect and counteracts the spontaneous progressive failure of these preparations (Bayliss, Mueller, and Starling). It seems likely that it promotes glycogen storage by the heart, and the cardiotonic effect may be related to the concomitant migration of potassium into the cells. Detailed investigations on this matter have not been found in the literature, moreover, there is no evidence that this is a significant regulatory mechanism. At present, it seems to be incidental to the general action of insulin on the cellular handling of glucose.

Gonads and Tropic Hormones. The cyclic influence of these substances on the vessels of the uterine mucosa during menstruation and gestation, though important, is incidental to the reproductive function and is more properly considered as such. This increased vascularity, which causes an increased pelvic blood flow, acts to some extent as an arteriovenous shunt and has been considered an important vasodynamic change in pregnancy. The same phenomenon, by raising pelvic venous pressure and further by causing congestion within the pelvic cage, tends to impair the return of blood through the pelvic veins and often precipitates the formation of *vulval or saphenous varices*. There is not enough evidence for the suggestion that the same chemical mechanism which causes vascular proliferation in the uterus may be responsible for a direct action on the veins of the lower extremity.

MISCELLANEOUS

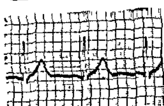
Under this heading are grouped those substances which seem to deserve little mention and those whose vascular significance is not yet clear enough for other classification

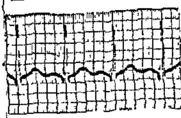
Serotonin. This substance, also known as 5-hydroxytryptamine, enteramine, thrombocytin, and thrombotonin, is found naturally in blood It may be extracted from plasma as a complex of equimolecular parts of creatine, sulfuric acid, and 5-hydroxyindole base, and is a *powerful vasoconstrictor* It has been known for 80 or more years that there was a vasoconstrictor power present in blood when it clots, and that this power does not appear when blood is prevented from clotting by sodium citrate

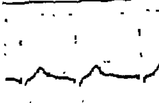
One of the factors causing the appearance of

WITHOUT ATROPINE

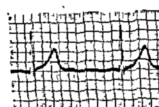
WITH ATROPINE

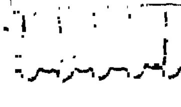












* T.P. = Tension Period, thousandths of a second
** E.P. = Ejection Period, thousandths of a second

Fig. 2-94. Infused, circulating norepinephrine causes bradycardia through a vagal reflex. Atropine, by eliminating this reflex, reveals the specific accelerating action of norepinephrine, which includes a shortening of the "tension period," T.P., of cardiac contraction.

crease of myocardial contractility and excitability. Concomitantly, the coronary blood flow is augmented, probably because of the marked metabolic and dynamic changes which occur in the myocardium under catecholamine influence.

Much confusion has arisen because peripherally injected norepinephrine elicits bradycardia. This phenomenon is due to the vasoconstrictor effect of norepinephrine, which, by raising the diastolic blood pressure, stimulates the pressoreceptors, thus causing a predominant vagal reflex that slows the heart action. Atropinization uncovers the specific acceleratory properties of norepinephrine (Fig. 2-94). Pathogenically, the most important cardiac effects of the catecholamines are those concerning myocardial oxygen consumption and "efficiency" (percentage of oxidative energy converted into mechanical work). Both epinephrine and norepi-

TABLE 2-10 EFFECTS OF NEUROHORMONES ON MYOCARDIAL METABOLISM

Type of neurohormones	*Oxygen consumption*	*Energetic efficiency*	*Glycogen*	*Lactic acid*	*Phosphocreatine*	*ATP*	*ATP-ase activity*	*Intracellular*	
								Na^+	*K^+*
Catecholamines									
Small doses	↑	↓	=	=	=	=	=	=	=
Large doses	↑	↓	↓	↑	↓	↓	=	↑	↓
Acetylcholine	↓	↑	↑	=	?	?	=	?	↑

belongs more properly under nervous control of the cardiovascular system.

CONCLUSION

Apparently, many of the naturally acting cardiovascular chemicals *can be thought of as* acting widely to adjust the cardiovascular *status* to various physiologic *occurrences which involve* many parts of the body and circumstances *that recur frequently in individual or phylogenetic history*. Some of those discussed in this *chapter* were somatic emergency (fight or flight reaction) mediated by the adrenal medulla, *drought*, by the posterior pituitary lobe; *physical activity*, by the metabolites, mineral *emergencies*, by the adrenal cortex; reproduction, by the vascular manifestations of the whole *suite* of sex endocrines; and perhaps shock and *hemorrhage*, by the renal pressor mechanisms.

These concepts are tentative and subject to revision as *new knowledge appears*, but at present they serve at least to provide some *threads* of continuity through an otherwise unmanageable mass of phenomena

CARDIOVASCULAR EFFECTS OF NEUROHORMONES AND HORMONES

The functional relationships between the *neurohormones* (norepinephrine, epinephrine, and acetylcholine), on the one hand, and certain glandular *hormones* (especially the thyroid hormone, the adrenal corticoids, and the pituitary adrenocorticotropic hormone), on the other, are so intimate that the cardiovascular effects of any of them can be properly evaluated and understood only by considering the interplay of each with its respective partners and antagonists.

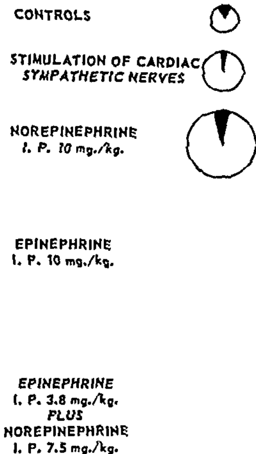


Fig. 2-93. Norepinephrine (white) and epinephrine (black) content of the dog's heart muscle. Electrical stimulation of the cardiac sympathetic nerves increases myocardial norepinephrine. Injected norepinephrine and epinephrine are absorbed by the myocardium. (*From Raab, 1956.*)

Adrenosympathetic Neurohormones (Catecholamines). Most of the cardiovascular responses to sympathetic nerve stimulation which were formerly attributed to a liberation of epinephrine are now known to be caused by the local discharge of *norepinephrine (arterenol)* from postganglionic sympathetic nerve endings directly into their respective myocardial or vascular muscular "effector cells." O. Loewi's *Sympathikusstoff* and Cannon's "sympathin E" have been identified by von Euler as norepinephrine, which is probably also identical with Haberlandt's *Herzhormon* It differs from epinephrine chemically only by the absence of a methyl group at the side chain.

The adrenal medulla discharges prevailingly epinephrine into the blood circulation, especially under stressful conditions. By contrast, the heart muscle and the vascular walls contain at all times appreciable quantities of norepinephrine, accompanied by small amounts of epinephrine Part of the myocardial catecholamine stores are believed to be synthesized within the heart muscle itself (Day). Stimulation of the cardiac sympathetic nerves is followed by an increase of the myocardial norepinephrine content (Fig 2-93); sympathetic denervation, by a decrease.

The direct specific actions of epinephrine and norepinephrine upon the heart consist of an acceleration of the heart rate and of the velocity of AV conduction, together with an in-

discharged at the parasympathetic cardiac nerve endings in the vicinity of the SA and AV nodes Inactive acetylcholine, stored in the heart muscle, can be liberated by electrical energy(?), destroyed by cholinesterase, and resynthesized by choline acetylase. It is believed to serve as an *essential link in the process of myocardial contraction*

The effects of acetylcholine on the heart are identical with those of vagal stimulation. They consist of slowing of the heart rate and of AV conduction, of a questionable negative inotropic action, and of an *oxygen-preserving, efficiency-increasing interference in the oxidative metabolism of the myocardium* The latter is directly opposed to the action of the sympathetic catecholamines Coronary flow is somewhat diminished by cholinergic action but not sufficiently to offset the oxygen gain caused by the metabolic influence of acetylcholine

A proprioceptive reflex mechanism originates in the heart muscle itself and causes an intensified parasympathetic cholinergic effect on the heart (*von Bezold-Jarisch reflex*).

Circulating acetylcholine stimulates, by virtue of its "nicotinic" properties, both sympathetic and parasympathetic ganglia, thus producing combined "amphomimetic" effects It also seems to provoke the discharge of catecholamines from intracardiac chromaffin cells

Vasodilator cholinergic fibers have been described, accompanying sympathetic pathways which supply the peripheral vasculature.

Thyroid Hormone. The thyroid hormone (thyroxin and triiodothyronine) accelerates the heart rate, intensifies the vigor of cardiac contraction, and augments myocardial oxygen consumption at the expense of energetic efficiency (Whitehorn and Ullrick) Even though its actions on the heart resemble those of the catecholamines, it seems that the metabolic and cardiovascular effects of the thyroid hormone are mediated by and dependent on catecholamine action (Brewster et al.) In any event, the cardioacceleratory, inotropic, calorigenic, and intermediary metabolic effects of sympathetic stimulation (norepinephrine discharges) and of epinephrine are greatly intensified by pretreatment with thyroid hormone, while they are weakened or abolished in its absence

Despite a certain potentiating influence of the thyroid hormone on the vascular effects of epinephrine and norepinephrine, its action on the blood pressure is not marked, except for an increase of pulse pressure due to augmentation of the stroke volume of the left ventricle.

The catecholamine-destroying tissue amine *oxidase* is believed to be reduced by the thyroid hormone.

Adrenal Corticoids. Cardiac rate and contractility are not acutely and strikingly affected



Fig 2-96 Vascular desensitization through dietary sodium withdrawal In a hypertensive individual, the pressor elevations caused ... epinephrine a ... sodium free (r ... the pressor e... of the catecholamines as much as under a normal regime (compare with Fig 2-95) Resumption of the latter gradually restores vascular reactivity. (*From Raab et al Circulation*, 1952)

nephrine increase remarkably the oxygen consumption of the heart muscle (Table 2-10). This phenomenon occurs as a result of the discharge of adrenal epinephrine and of sympathetic neurogenic norepinephrine. In contrast to a widespread belief, it is not essentially dependent on an association with augmentation of cardiac work. The extra amount of oxygen *consumed by the heart muscle under the unopposed influence of the catecholamines* greatly exceeds that portion which is needed for the additional mechanical work *the catecholamines waste oxygen and reduce cardiac energetic efficiency* They are even capable, under certain conditions, of augmenting myocardial oxygen consumption without any increase of mechanical work. However, this seemingly paradoxical wastage is normally compensated by cholinergic vagal counteraction, which preserves oxygen and increases efficiency (Table 2-10)

The norepinephrine deposits in the vascular walls, which are constantly replenished from the postganglionic nerve endings, maintain the local vascular tonus and blood pressure homeostasis. Norepinephrine, introduced into the general circulation, acts an an over-all vasoconstrictor, with the exception of the coronary and cerebral vessels. It raises both the systolic and *the diastolic pressure. Circulating epinephrine*, on the other hand, causes vasodilatation in large sections of the arterial tree, especially in the striated musculature, thus lowering peripheral resistance and diastolic pressure. Its positive pressor effect, which concerns prevailingly or exclusively the systolic level, is chiefly due to an increase of cardiac output (stroke volume). The renal arterioles are constricted both by norepinephrine and epinephrine.

Acetylcholine. Apart from its function as a ganglionic synaptic transmitter, acteylcholine is

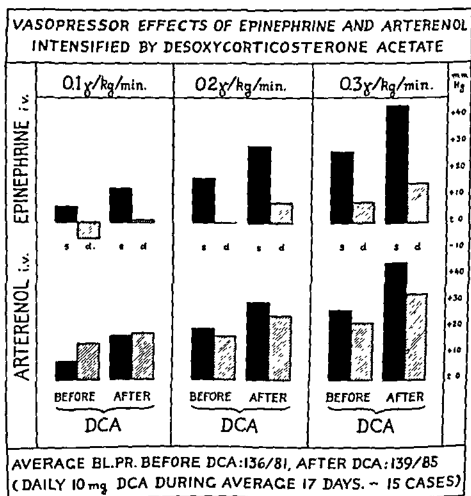


Fig. 2-95. Potentiation of vascular pressor responsiveness to catecholamines through desoxycorticosterone acetate. Deviations of the systolic (black) and diastolic (shaded) blood pressures of 15 normotensive subjects during intravenous infusion of epinephrine and norepinephrine at different dosage levels before and after administration of DCA. (From Raab et al J. Clin. Invest. 1950.)

30

The emotions, the hypothalamus, and the cardiovascular reactions

ERNST GELLHORN

The influence of the hypothalamus on cardiovascular reactions is well established on the basis of classic investigations of Karplus and Kreidl, Beatty, Ranson, and Hess

Stimulation of the *anterior* hypothalamus elicits chiefly parasympathetic effects, whereas that of the *posterior* hypothalamus is mostly followed by sympathetic effects. However, the characteristics of the currents used for stimulation must be taken into account Since the emotions involve the hypothalamus, and emotional processes are accompanied by autonomic reactions in general and cardiovascular reactions in particular, it is generally assumed that the autonomic discharges occurring during emotional excitation are, at least in part, of hypothalamic origin

The importance of the study of the emotions for neurophysiology, psychology, and medicine has resulted in numerous physiologic and clinical investigations, which not only shed new light on the fundamental role of the hypothalamus in cardiovascular reactions, but also resulted in the development of methods by which the state of the hypothalamus can be ascertained in the intact organism In addition, new facts have been disclosed on the secretion and excretion of neurohumors in different emotional states

PHASIC VASCULAR REACTIONS DEPENDING ON THE HYPOTHALAMUS

It is known (Hering, Heymans, Koch, and many others) that alterations of the pressure in the sinoaortic area, and consequently of the blood pressure, lead to characteristic changes in parasympathetic and sympathetic discharges. A fall in pressure causes a diminution, and a rise in pressure, an increase in the parasympathetic reflex discharges which originate in the pressoreceptors of the sinoaortic area Sympathetic discharges are reciprocally related to the parasympathetic discharges under these conditions A fall in sinoaortic pressure leads, therefore, to increased sympathetic effects. These changes in the autonomic balance occur not only when the pressure in the isolated carotid sinus is altered but also when hypotensive or hypertensive drugs are administered. An injection of acetylcholine, Mecholyl, or histamine causes a sympathetic discharge indicated by the contraction of the nictitating membrane (n.m) and the acceleration of the heart rate. Conversely, an injection of norepinephrine or epinephrine is accompanied by a slowing of the heart rate, which reveals the increased parasympathetic discharges that are induced by the rise of the blood pressure. The following experiments show that these autonomic effects are significantly altered by changes in the state of the hypothalamus (Gellhorn, 1956).

The experimental setup was as follows: the blood pressure, heart rate, and the movements of the normal and denervated n m. were recorded in the lightly anesthetized cat. Then one of the above-mentioned hypotensive drugs was injected intravenously This caused a temporary drop of blood pressure As the blood pressure recovered from

by the adrenal corticoids. However, depression of the S-T segment and the T wave, and, in adrenalectomized animals, a correction of the dynamic weakness of the heart, can be produced by administration of desoxycorticosterone acetate (DCA) and cortical extracts. The inotropic effect of epinephrine on the heart was found intensified by DCA. The changes of cardiac dynamics under the influence of DCA are probably due to the effect of the latter on myocardial electrolyte distribution (intracellular increase of sodium, loss of potassium).

More impressive, although slowly developing, is the blood pressure–elevating action of the mineralocorticoids. It requires the presence of certain minimum amounts of both sodium and potassium in the body and is markedly intensified by the intake of extra sodium. Here, too, the (vascular) catecholamines seem to be significantly involved, as suggested by the DCA-induced intensification of the pressor effects of both epinephrine and norepinephrine (Fig. 2-95). Since this phenomenon is likewise dependent on an adequate sodium supply (Fig. 2-96), it is being assumed that the mineralocorticoids sensitize the vascular walls to the depolarizing pressor amines by their primary influence on the intra- and extracellular cationic gradient. This factor, in turn, determines the electric membrane potential of the contractile cells and their contraction amplitude Thus, the problem of hormonal blood pressure regulation may be considered as basically physicochemical (Friedman and Friedman).

Cortisone sensitizes the vascular walls to the constrictor action of the catecholamines more rapidly than DCA, possibly by influencing cellular carbohydrate metabolism and potassium transfer.

Gonadal Steroids. Neither the male nor the female sexual hormones exert any clearly defined direct influence on mammalian cardiac and vascular dynamics and metabolism

Somatotropic (Growth) Hormone of the Pituitary Gland. The growth hormone seems to participate in the development and maintenance of the cardiac muscular mass In the presence of extra amounts of sodium, growth hormone is capable of elevating the blood pressure.

Posterior Pituitary Hormone. The posterior pituitary hormone (*vasopressin*) elevates the blood pressure through general vasoconstriction, and it also constricts the coronary arteries. However, a physiologic significance of these effects is doubtful.

Insulin. Insulin does not produce any clearly specific effects on the cardiovascular functional state but if present in excess, elicits discharges of epinephrine with corresponding cardiovascular reactions

Parathyroid Hormone. The parathyroid hormone shortens the electrical systole by raising the serum calcium level.

rine was greatly diminished. Since the pulse-slowing reflex depends, other conditions being equal, on the rise of the blood pressure, it is important to mention that the pressor effect of norepinephrine was not infrequently increased when the excitability of the anterior hypothalamus was reduced. The diminished reflex slowing of the heart rate under these conditions represents, therefore, a proof for the dependence of this parasympathetic reflex on the anterior hypothalamus These results were confirmed by experiments in which lesions were produced in the area of the anterior hypothalamus which is between the optic chiasma and the anterior commissure. In agreement with the previously described experiments involving the posterior hypothalamus, it was found that the action of barbiturates on the anterior hypothalamus produced reversible results, whereas the change produced by high-frequency lesions was irreversible for the duration of the experiment

Earlier work indicated that the principle of reciprocal innervation established by Sherrington for the somatic nervous system holds true for autonomic reflexes involving the medulla oblongata. More recent studies (Gellhorn, 1956) show that this principle is valid for intrahypothalamic autonomic functions Two groups of experiments may be cited In the first group, the drug-induced hypotensive action was studied before and after lesions had been produced in the *anterior* hypothalamus Such lesions led to an increase in the sympathetic effects accompanying the hypotensive action, in a lessening of the hypotensive area, and in the occurrence of a brief secondary hypertensive effect that was absent under control conditions. The diminution of parasympathetic reflex excitability characteristic for the effect of anterior hypothalamic lesion is, therefore, associated with a release of the sympathetic discharges of the posterior hypothalamus indicated by the described alterations of the action of hypotensive drugs.

Similarly, *posterior* hypothalamic lesions lead not only to a diminished sympathetic reactivity (tested by hypotensive drugs), but also to a release of the anterior hypothalamus, indicated by an intensification of the pulse-slowing reflex in response to a given rise of the blood pressure (induced by norepinephrine) The parasympathetic reflex was thus found to be stronger than under control conditions (Table 2-11)

This experimental work proves that *alterations in the state of excitability of the anterior and posterior hypothalamus are accompanied by characteristic changes in the autonomic reflexes following a drug-induced rise or fall of blood pressure* These facts suggest a direct relation between the pressoreceptor reflexes, elicited by the drug-induced changes in the blood pressure, and the hypothalamus This statement is supported by the following experiments.

Stimuli acting on the posterior hypothalamus exert a diffuse excitatory action on the cerebral cortex characterized by an increased asynchrony and frequency of cortical potentials. This excitatory action is greatly reduced at the

TABLE 2-11 EFFECT OF LESIONS IN THE HYPOTHALAMUS ON THE ACTION OF HYPOTENSIVE DRUGS AND THE NOREPINEPHRINE-INDUCED PULSE-SLOWING REFLEX

Location of lesion	*Hypotensive drugs*	*The norepinephrine-induced pulse-slowing reflex*
Anterior hypothalamus	Increase of sympathetic discharges indicated by the n m. and pulse rate Diminution of hypotensive area Appearance of a secondary hypertensive phase	Diminution or abolishment of the reflex (often in spite of increased rise of the blood pressure in response to norepinephrine)
Posterior hypothalamus	Decrease of sympathetic discharges indicated by the n m and pulse rate Increase of hypotensive area	Increase of the pulse-slowing reflex

the hypotension, the heart rate was accelerated and the normal n.m. contracted. These signs indicated the sympathetic discharge resulting from the temporary drop in intrasinusal pressure. If the preparation was very sensitive, a contraction of the denervated n.m. appeared, indicating that a neurohormone (epinephrine or norepinephrine) had been released from the adrenal medulla. Ligation of the adrenal veins prevented the contraction of the denervated n.m. upon administration of a hypotensive drug.

The influence of the state of excitability of the hypothalamus on this action of hypotensive drugs was striking. When minute amounts of Pentothal were injected with microneedles into the posterior hypothalamus (Gellhorn, 1955), the excitability of this structure to electrical stimulation was diminished and the reaction to the injection of a hypotensive drug was characteristically altered. The contraction of the n.m. and the degree of acceleration of the heart rate were diminished. If a contraction of the denervated n.m. had occurred during the action of the hypotensive drug under control conditions, it was likewise reduced or abolished after the intrahypothalamic injection of a barbiturate. At the same time it was found that the recovery of the blood pressure from the drug-induced hypotension was delayed. After about 30 to 40 min, the effect of Pentothal wore off, the electrical excitability of the posterior hypothalamus was partially or completely restored, and, parallel with this restitution, the action of the hypotensive drug became similar to that recorded under control conditions.

Numerous experiments of this kind showed clearly that (1) the action of a hypotensive drug elicits a sympathetic or sympathoadrenal discharge, (2) the intensity of this discharge is lessened when the excitability of the posterior hypothalamus is diminished, (3) parallel with the diminution of the sympathetic discharge, the action of the hypotensive drug becomes prolonged and the hypotensive area [1] is increased.

Similar results were obtained when, through high-frequency coagulation, a bilateral lesion was produced in the posterior hypothalamus (Gellhorn, 1956). In this case, however, the reduction in the sympathetic discharges and the increase in the hypotensive area in response to a hypotensive drug were not reversible.

The fundamental importance of the state of excitability of the posterior hypothalamus for the action of hypotensive drugs is further illustrated by experiments in which the excitability of this structure was increased. For this purpose, Metrazol or strychnine was injected *in minute quantities into the posterior hypothalamus*. The sympathetic reactions, indicated by the n.m. and by the heart rate changes which accompany the action of hypotensive drugs, were increased. At the same time, the return of blood pressure from the drug-induced hypotension was accelerated. Moreover, the blood pressure showed temporarily a hypertensive phase after the initial phase of hypotension. These alterations were likewise reversible. Finally, it was shown that a reduction in the hypotensive area, a secondary hypertensive phase, and an increase in the height of contraction of the n.m. and in the heart rate, indicative of increased sympathetic discharges, occur upon injection into a cat of a hypotensive drug in the following circumstances (Redgate and Gellhorn, 1953): (1) during awakening of the cat indicated by spontaneous movements, pupillary dilatation, and contraction of the normal n.m., (2) during the inhalation of 5 to 8 per cent carbon dioxide; (3) during electrical subthreshold or threshold stimulation of the posterior hypothalamus.

These effects were accompanied by an increased sympathetic responsiveness of the posterior hypothalamus to electrical stimulation and were completely reversible.

The investigations described above seem to indicate that *the state of excitability of the posterior hypothalamus exerts a significant influence on the sympathetic discharges accompanying the action of hypotensive drugs and on the blood pressure effect produced by them.* It was, therefore, expected that parasympathetic reflexes elicited by a rise in blood pressure would show a similar dependence on the state of excitability of the anterior hypothalamus. This is indeed the case (Redgate and Gellhorn, 1956). When minute amounts of Pentothal or Nembutal were injected into the anterior hypothalamus, the pulse-slowing reflex induced by the rise of blood pressure resulting from the intravenous injection of norepineph-

[1] Changes in hypothalamic excitability influence primarily the rate of recovery from the drug-induced hypotensive effect. When the recovery is delayed (as after reduction of the excitability of the posterior hypothalamus), the *hypotensive area*, which is determined by the preinjection level of the blood pressure and by the blood pressure curve until the control level is reached again, is considerably enlarged.

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Anterior hypothalamus	Increase of sympathetic discharges indicated by the n m and pulse rate Diminution of hypotensive area Appearance of a secondary hypertensive phase	Diminution or abolishment of the reflex (often in spite of increased rise of the blood pressure in response to norepinephrine)
Posterior hypothalamus	Decrease of sympathetic discharges indicated by the n m and pulse rate Increase of hypotensive area	Increase of the pulse-slowing reflex

the hypotension, the heart rate was accelerated and the normal n.m. contracted. These signs indicated the sympathetic discharge resulting from the temporary drop in intrasinusal pressure. If the preparation was very sensitive, a contraction of the denervated n.m. appeared, indicating that a neurohormone (epinephrine or norepinephrine) had been released from the adrenal medulla. Ligation of the adrenal veins prevented the contraction of the denervated n.m. upon administration of a hypotensive drug.

The influence of the state of excitability of the hypothalamus on this action of hypotensive drugs was striking. When minute amounts of Pentothal were injected with microneedles into the posterior hypothalamus (Gellhorn, 1955), the excitability of this structure to electrical stimulation was diminished and the reaction to the injection of a hypotensive drug was characteristically altered. The contraction of the n.m. and the degree of acceleration of the heart rate were diminished. If a contraction of the denervated n.m. had occurred during the action of the hypotensive drug under control conditions, it was likewise reduced or abolished after the intrahypothalamic injection of a barbiturate. At the same time it was found that the recovery of the blood pressure from the drug-induced hypotension was delayed. After about 30 to 40 min, the effect of Pentothal wore off, the electrical excitability of the posterior hypothalamus was partially or completely restored, and, parallel with this restitution, the action of the hypotensive drug became similar to that recorded under control conditions.

Numerous experiments of this kind showed clearly that (1) the action of a hypotensive drug elicits a sympathetic or sympathoadrenal discharge, (2) the intensity of this discharge is lessened when the excitability of the posterior hypothalamus is diminished, (3) parallel with the diminution of the sympathetic discharge, the action of the hypotensive drug becomes prolonged and the hypotensive area[1] is increased.

Similar results were obtained when, through high-frequency coagulation, a bilateral lesion was produced in the posterior hypothalamus (Gellhorn, 1956). In this case, however, the reduction in the sympathetic discharges and the increase in the hypotensive area in response to a hypotensive drug were not reversible.

The fundamental importance of the state of excitability of the posterior hypothalamus for the action of hypotensive drugs is further illustrated by experiments in which the excitability of this structure was increased. For this purpose, Metrazol or strychnine was injected in minute quantities into the posterior hypothalamus. The sympathetic reactions, indicated by the n.m. and by the heart rate changes which accompany the action of hypotensive drugs, were increased. At the same time, the return of blood pressure from the drug-induced hypotension was accelerated. Moreover, the blood pressure showed temporarily a hypertensive phase after the initial phase of hypotension. These alterations were likewise reversible. Finally, it was shown that a reduction in the hypotensive area, a secondary hypertensive phase, and an increase in the height of contraction of the n.m. and in the heart rate, indicative of increased sympathetic discharges, occur upon injection into a cat of a hypotensive drug in the following circumstances (Redgate and Gellhorn, 1953): (1) during awakening of the cat indicated by spontaneous movements, pupillary dilatation, and contraction of the normal n.m., (2) during the inhalation of 5 to 8 per cent carbon dioxide, (3) during electrical subthreshold or threshold stimulation of the posterior hypothalamus.

These effects were accompanied by an increased sympathetic responsiveness of the posterior hypothalamus to electrical stimulation and were completely reversible.

The investigations described above seem to indicate that *the state of excitability of the posterior hypothalamus exerts a significant influence on the sympathetic discharges accompanying the action of hypotensive drugs and on the blood pressure effect produced by them.* It was, therefore, expected that parasympathetic reflexes elicited by a rise in blood pressure would show a similar dependence on the state of excitability of the anterior hypothalamus. This is indeed the case (Redgate and Gellhorn, 1956). When minute amounts of Pentothal or Nembutal were injected into the anterior hypothalamus, the pulse-slowing reflex induced by the rise of blood pressure resulting from the intravenous injection of norepineph-

[1] Changes in hypothalamic excitability influence primarily the rate of recovery from the drug-induced hypotensive effect. When the recovery is delayed (as after reduction of the excitability of the posterior hypothalamus), the *hypotensive area,* which is determined by the preinjection level of the blood pressure and by the blood pressure curve until the control level is reached again, is considerably enlarged.

the heart rate, is determined chiefly by the state of hypothalamic excitability, the Mecholyl and norepinephrine tests should disclose the state of sympathetic and parasympathetic excitability of the hypothalamus in the intact organism and also the state of autonomic balance. Moreover, factors which influence the state of the hypothalamus (emotions, drugs) should lead to characteristic quantitative changes in these tests

This statement is supported by the following observations

1 Changes in the emotional state are accompanied by corresponding alterations in the Mecholyl-induced blood pressure curve (Funkenstein, Silverman et al).

2 Small concentrations of barbiturates known to depress the reactivity of the hypothalamus alter the blood pressure response to Mecholyl as if the excitability of the posterior hypothalamus had been lowered, the hypotensive action of Mecholyl is increased in the experimental animal and also in man

The *application* of the Mecholyl test (10 mg intramuscularly) to normal persons and neuropsychiatric patients has shown that three types of reactions can be distinguished on the basis of the blood pressure response to this drug *Type I* shows a slight hypotension followed by a prompt return to base-line readings with a subsequent overshooting above the previous resting levels *Type II* shows a *moderate* hypotension with return to control level within 8 to 10 min, with no overshooting *Type III* shows a *marked* hypotension with delayed return to previous base-line levels

In the light of the experimental studies mentioned above, type I seems to represent *increased* posterior (sympathetic) hypothalamic reactivity, *type II, normal*, and type III, *decreased* reactivity.

The Mecholyl curve changes with increasing age from type I to type III, suggesting that the sympathetic reactivity, presumably at the hypothalamic level, diminishes progressively A similar decrease of the parasympathetic reactivity occurs with increasing age This can be determined by the norepinephrine-induced slowing of the heart rate and can be measured by the quotient

$$\frac{\text{Mean of resting pulse rates minus minimal pulse rate}}{\text{Maximal systolic blood pressure minus mean of resting systolic blood pressures}}$$

These findings suggest that the central autonomic reactivity is altered as age advances but that no imbalance is involved. Further studies of Nelson and Gellhorn showed indeed that the frequency of autonomic imbalance as determined by the Mecholyl and norepinephrine tests is small in so-called normal individuals but large in the neuropsychiatric group.

It will be of great interest to use these tests in cases of hypertension, Raynaud's disease,* and various central disturbances of the autonomic nervous system, and to correlate the therapeutic effects with these autonomic tests. See Gellhorn (1953c) for a similar suggestion concerning the therapy of functional mental disorders.

TONIC VASCULAR REACTIONS DEPENDING ON THE HYPOTHALAMUS

The work described in the first part of this chapter presented evidence that vascular reflexes known to be mediated by the medulla oblongata involve the hypothalamus. Since the medulla oblongata is said to be the "center" not only of sympathetic and parasympathetic reflexes but also of important tonic functions which determine blood pressure level and heart rate, the question arises as to what extent tonic-vascular functions are attributable to the hypothalamus. The answer to this question is based on experiments similar to those described earlier in the chapter Lesions confined to the anterior or posterior hypothalamus, respectively, showed definite effects on blood pressure and heart rate Here again, the injection of Pentothal or Nembutal into various parts of the hypothalamus was utilized to produce lesions with reversible effects, whereas *irreversible* lesions were obtained by means of high-frequency currents Aside from the difference in reversibility, the physiologic effects of the two procedures were similar

Figure 2-97 shows that the injection of Pentothal into the posterior hypothalamus causes a fall of blood pressure and, at the same time, a slowing of the heart rate. About 25 min later, the blood pressure and heart rate return to nearly preinjection levels. The sites of injection from which these effects can be obtained are located *in* and near the mammillary bodies and the *infundibular* region (Fig. 2-98). This area is likewise responsible for the decrease of blood pressure and heart rate observed after high-frequency lesions

* *It* is noteworthy that, in both conditions, emotional disturbances are frequent

ipsilateral side of the cortex after unilateral hypothalamic lesions. Similar findings result from the action of the drug-induced hypotension. If, for instance, a small amount of acetylcholine or Mecholyl is injected intravenously in a very lightly anesthetized cat, the recovery of the blood pressure from the hypotension is accompanied by a diffuse excitation of the cortex. This excitation is greatly reduced or abolished ipsilaterally after a unilateral hypothalamic lesion.

Further experiments serve to clarify the mechanism by which the drug-induced hypotension calls forth a hypothalamic-cortical discharge leading to the described diffuse cortical excitation. For this purpose, the action of hypotension on cortical potentials before and after denervation of the sinoaortic area must be considered. It was found that after elimination of the receptors in the sinoaortic area, the drug-induced hypotension failed to elicit the diffuse excitation of the cortex which is regularly found in the normal animal (Nakao et al.).

The effect of a drug-induced hypotension on the hypothalamus is disclosed by direct tests of its excitability and the study of the electrical activity of the posterior hypothalamus. When this structure is tested with an electrical stimulus as the blood pressure begins to recover from the hypotension, a greater sympathetic effect is elicited than under control conditions. In addition, the frequency analysis of the potentials shows that hypotension calls forth an excitation of the posterior hypothalamus

Analogous experiments on the action of hypertensive drugs (norepinephrine) may be summarized as follows:

1. The excitability of the posterior hypothalamus is lessened when an electrical stimulus is applied during the height of the norepinephrine-induced hypertension.

2. The injection of norepinephrine causes a diminution in the excitability of the cerebral cortex, since grouped potentials appear as in sleeplike conditions.

3 This diminution in cortical excitability does not occur when norepinephrine is injected in the sinoaortic denervated cat.

4 The frequency analysis of the potentials in the posterior hypothalamus of a normal cat discloses a shift which is characteristic for states of diminished excitability

It is concluded from these experiments that hypotensive drugs cause an excitation of the posterior hypothalamus, whereas hypertensive drugs cause a reduction in hypothalamic excitability through reflex action via the sinoaortic pressoreceptors. In the former instance, the hypothalamic-cortical discharge is increased, whereas it is decreased in the latter case

THE ROLE OF HYPOTHALAMUS AND MEDULLA OBLONGATA IN PRESSORECEPTOR REFLEXES

It has been stated that the drug-induced pressoreceptor reflexes act on the hypothalamus. Moreover, the state of excitability of the anterior and posterior hypothalamus exerts a great influence on the intensity of these reflexes On the other hand, pressoreceptor reflexes occur in the decerebrate animal, proving that they do not require the presence of the diencephalon These data raise the question of the relation existing between hypothalamus and medulla oblongata and the relative importance of these two structures for the pressoreceptor reflexes.

When, as the result of lesions in the posterior hypothalamus, the sympathetic response to a lowering of the blood pressure through hypotensive drugs (or other means) has been diminished or has disappeared, it may still be evoked by a stronger stimulus (for instance, a stronger concentration of the hypotensive drug). Similar observations were made after the pulse-slowing reflex occurring in response to a certain dose of norepinephrine had disappeared after a lesion of the anterior hypothalamus. It may, therefore, be said that, *although the hypothalamus is not necessary for the pressoreceptor reflexes controlling cardiovascular reactions, it determines the threshold of these reflexes*[2] *Moreover, the quantitative response to suprathreshold stimuli appears to be determined by the state of excitability of the hypothalamus.*[3]

These findings have an important application for clinical medicine Since the action of a hypotensive drug, such as Mecholyl on the blood pressure, and that of norepinephrine on

[2] The greater sensitivity of the hypothalamus as compared with that of the medulla oblongata may be related to its greater metabolism (emphasized by Himwich et al).

[3] On the basis of Bronk's work, it may be assumed that variations in the intensity of the sympathetic discharge are brought about by corresponding changes in the number of the discharging neurons and the rate of discharge of the individual neurons.

humors of the sympathoadrenal system. It is now agreed that, in general, the stimulation of sympathetic nerves or the excitation of sympathetic "centers" leading to sympathetic discharges causes a liberation of norepinephrine When the splanchnic nerves are stimulated or sympathetic centers are stimulated causing the excitation not only of the sympathetic nerves supplying the heart and blood vessels but also of the adrenal medulla, norepinephrine and epinephrine appear in the blood stream in varying quantities and are excreted in the urine in increased amounts

The following methods have been used as indicators of the liberation of these neurohumors.

1. The analysis of the blood for norepinephrine and epinephrine based on chemical methods and on bioassay. These techniques have been used largely in physiologic experiments

2. The assay of norepinephrine and epinephrine in the urine

3. The study of the vascular changes occurring during stress and emotional excitation This method is based on the fact that the effects of norepinephrine and epinephrine on the peripheral vascular resistance and on the output of the heart are fundamentally different

The last two methods have been used extensively in the study of the emotions in man

Funkenstein made his *observations* on "normal" persons and neuropsychiatric patients largely on the basis of the third method and other indirect indicators He came to the interesting conclusion that *resentment* (the persons were "angry at others") *seemed to lead to the liberation of norepinephrine* whereas states of *fear* and *anxiety* (they were "angry at themselves") *appeared to be associated with the liberation of epinephrine* These investigations were confirmed in studies of Silverman et al, in which stressful situations led *to anger* and fear, respectively. In this work, the excretion of the neurohumors appeared to be specifically related to the type of emotion, as in Funkenstein's observations To explain these results, Funkenstein (1955) advanced the thesis that the excitation of certain areas of the hypothalamus leads to *fearlike reactions*, whereas others produce *ragelike effects* The former lead to the liberation of epinephrine, the latter to that of norepinephrine This hypothesis appears to be untenable for several reasons Although experiments of the Hess school indicate that stimulation of different sites of the hypothalamus may evoke aggressive and escape-like reactions interpretable as anger and fear, respectively, it is quite evident from Hunsperger's study that there is an extensive overlap between these sites. Moreover, the pinpoint-like localization of complex psychic functions in the brain has been discredited since von Monakow's work (1914).

Two groups of data require a physiologic interpretation. (1) that anger leads to the liberation of norepinephrine and fear to that of epinephrine; (2) that persons in the state of anger show in response to Mecholyl the type I reaction, whereas the type III reaction is characteristic for persons in the state of fear. In the light of the previously discussed experiments, this indicates that the state of hypothalamic sympathetic excitability is high in anger and low in fear.

Since the appearance of epinephrine in the blood or urine is almost certainly an indication of adrenomedullary secretion, it would seem that *a state of low hypothalamic excitability may be associated with a marked adrenomedullary secretion* This conclusion seems paradoxic, since it is generally assumed that mild reflex stimulation of the sympathetic system leads to sympathetic discharges, whereas under the influence of strong stimuli sympathoadrenal discharges appear Moreover, it was shown that weak stimulation of the posterior hypothalamus elicits sympathetic effects, whereas strong stimulation induces discharges involving, in addition, the adrenal medulla.

The solution of this puzzle seems to lie in the fact that the regulation of the secretory, epinephrine-producing activity of the adrenal medulla is primarily a function of the medulla oblongata, whereas excitation of the sympathetic division of the hypothalamus causes chiefly the liberation of norepinephrine from the nerve endings of the sympathetic system (and possibly from the adrenal medulla) This interpretation would fit the experimental fact that stimulation of the posterior hypothalamus leads to the liberation of norepinephrine, whereas prolonged asphyxia causes the appearance of epinephrine in the blood. In *asphyxia*, the excitability of hypothalamus and cerebral cortex *is* too low to contribute significantly to the sympathetic discharge, whereas that of the medulla oblongata is much less altered

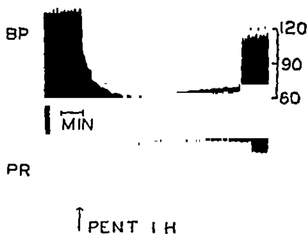


Fig. 2-97. Cat 235. 3 kg. The bilateral injection of Pentothal (0.04 ml, 4 per cent) into the posterior hypothalamus resulted in a fall of blood pressure and a decrease in pulse rate. After a 25-min pause, the blood pressure and pulse rate recovered, as seen at the end of the record Note that an increase in the amplitude of the record of the pulse rate (PR) indicates a slowing of the heart rate

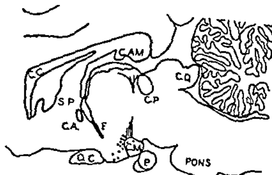


Fig. 2-98. Sagittal section (2.5 mm from the midline) through the cat's brain showing the sites of injection (black dots) of barbiturates and procaine into the hypothalamic region. The sites of injection were projected into the same plane although there were deviations from it up to 1 5 mm. C.A, Anterior commissure; C. AM., cornu ammonis; C.C, corpus callosum; C.M., corpus mammillare; C.P., posterior commissure; C.Q., corpora quadrigemina; F, fornix, O.C., optic chiasma; P., pituitary; S P., septum pellucidum

The experiments seem to indicate that *the posterior hypothalamus exerts a tonic sympathetic function on heart and blood vessels.* If, as the result of intrahypothalamic injection of a barbiturate, the blood pressure falls considerably, the pulse rate is accelerated As the pressoreceptor reflexes are still operative after the functional elimination of the hypothalamus, even though their threshold is increased, the acceleration of the heart rate appears only when the fall of the pressure is rather large In the experiments in which high-frequency currents caused only minimal lesions, the fall of blood pressure was smaller and was accompanied by a decrease of heart rate in practically all experiments. The significance of these findings for the problem of hypertension is obvious An emotional component in the genesis of essential hypertension is admitted by many authors

Schunk showed that a considerable percentage of cats exposed daily to barking dogs develop hypertension and an enlargement of the heart It is suggested that these changes are due to increase of the tonic sympathetic discharges originating largely in the posterior hypothalamus as a result of repeated excitation of this structure during emotional excitement [5] That autonomic centers have the tendency to undergo long-lasting changes in excitability as the result of repeated stimulations is well known.

Through the injection of barbiturates in the area between the optic chiasma and the anterior commissure, and through high-frequency coagulation of the nervous tissue in this area, the role of the anterior hypothalamus on blood pressure and heart rate was disclosed The effect of these procedures was less marked than when the posterior hypothalamus was involved. In the majority of the experiments, the decrease in the anterior hypothalamic excitability resulting from the application of the two procedures resulted in a rise of blood pressure and an increase in heart rate. *Apparently, the anterior hypothalamus exerts a tonic parasympathetic function on heart and blood vessels, although its intensity is less than the tonic sympathetic action of the posterior hypothalamus*

THE LIBERATION OF NOREPINEPHRINE AND EPINEPHRINE IN EMOTIONS

Physiologic studies between 1945 and 1955 have advanced understanding of the role of norepinephrine and epinephrine as neuro-

[5] The failure of Walker et al. (1954) to eliminate, through diencephalic lesions, the hypertension resulting from denervation of the carotid sinuses may be due to the fact that they did not study the effect of bilateral lesions in the posterior hypothalamus

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Dietary requirements of the human body

WILLIAM N. PEARSON

THE OPTIMUM DIET

By definition the optimum diet for the human being will contain adequate amounts of *water*, *protein*, and *energy* In addition, certain *minerals* need to be present in relatively large quantities, and accessory growth factors such as *vitamins* and essential *fatty acids* must be present in small amounts No single foodstuff will supply all these necessary nutrients in optimum amounts—therefore, the adequate diet is most often a varied diet and may be assembled from a wide variety of foodstuffs in accordance with availability, national food habits, individual tastes, and economic factors

The following discussion will deal with individual qualitative dietary requirements and the levels of intake as recommended by the Food and Nutrition Board of the National Research Council (1958)[1]

The reference man and woman, as defined by this group, are a man and woman, both aged 25, living in a temperate climate (mean annual external temperature 20°C) and weighing 70 and 58 kilograms, respectively These reference persons are presumed to be fairly active physically, being neither sedentary nor engaged in hard physical labor as a major occupation

The recommended allowances for adults and other age groups are shown in Table 2-12.

[1] *Recommended Dietary Allowances, Revised*, 1958, Publication 589, National Academy of Sciences, National Research Council, 36 pages

It should be emphasized that these recommended allowances are not minimum requirements but contain considerable margins of safety—"they represent, not merely minimal needs of average persons, but nutrient levels selected to cover individual variations in a substantial majority of the population."

Other dietary standards based on somewhat different philosophies have been formulated by official bodies in *Canada* (1950) and *Great Britain* (1950) In all cases the reader should be cautioned that dietary standards are never final and are subject to change as more knowledge becomes available. A decade from now the concept of the adequate diet may be radically altered

METHODOLOGY

Two general techniques have been used most often for the assessment of the quantitative and qualitative dietary needs of the human being. The first and least accurate method is to examine the intake of the nutrient in question in a seemingly healthy population and to record the intake found as compatible with good health This method was used long ago by Voit (1870), who studied the food habits of healthy Bavarian farmers and concluded that a desirable protein intake should be around 120 Gm per day Although this technique can be expected to yield reasonably reliable information, it does not permit one to establish whether or not a particular nutrient is essential.

The second method that has been employed to great advantage depends upon the preparation of purified complete diets which can be rendered deficient in one or another nutrient In this way, the

The data of the literature and systematic work on the alterations in a variety of conditions of the quotient

$$\frac{\text{Neurogenic (sympathetic) discharge}}{\text{Adrenomedullary discharge}}$$

are compatible with this hypothesis, as indicated by the following findings:

1. Nociceptive stimuli produce in the normal cat sympathetic effects on pupils and nictitating membrane which are the result of the production of norepinephrine from the sympathetic nerve endings Signs of adrenomedullary secretion (indicated by contraction of the denervated nictitating membrane) are absent In anesthesia, however, the effect of stimulation is reversed: the signs of adrenomedullary secretion predominate

2 A brief period of asphyxia elicits marked sympathetic discharges and no adrenomedullary secretion, whereas after prolonged asphyxia, the adrenomedullary secretion is large and signs of sympathetic excitation are slight or absent.

3 With progressing anesthesia, the effect of a brief period of asphyxia changes from a neurogenic response (based on the liberation of norepinephrine) into an adrenomedullary response

Moreover, severe hemorrhage, which abolishes cortical and diencephalic excitability, is associated with an excessive secretion of epinephrine from the adrenal medulla and high concentrations of carbon dioxide, which likewise reduce or eliminate the functions of the cortex and hypothalamus and increase considerably the secretion of the adrenal medulla.

On the basis of this evidence, it is assumed that the liberation of norepinephrine in conditions of emotional stress is associated with a state of high sympathetic hypothalamic excitability,[6] whereas in states of relatively low hypothalamic excitability, the secretion (and excretion) of epinephrine resulting from the increased activity of the medulla oblongata and spinal cord predominates.

In the light of this experimental work, the question must be raised as to which factors are responsible for the different states of sympathetic hypothalamic excitability in anger and fear. Clinical observations have shown that anger is associated with a marked increase in the tone of the striated muscles, whereas, in states of fear and terror, the muscle tone seems to be low. Now it is known that proprioceptive impulses activate the hypothalamus and indirectly the cerebral cortex and that their elimination by curare reduces hypothalamic and cortical excitability. Without discussing the cerebral mechanism underlying the different states of muscle tone in different emotions, it is suggested that the tone of the voluntary muscles in these emotional states is an important factor determining the relative excitability of the hypothalamus and medulla oblongata and thereby the type of secretion and excretion of the neurohumors.

[6] It is of interest that pain produced by the cold pressor test elicits a norepinephrine reaction This finding is in agreement with the author's interpretation, since the excitatory effect of nociceptive stimuli on the posterior hypothalamus and the hypothalamic-cortical system is well established.

NEUROHUMORS AND HOMEOSTASIS

The liberation of norepinephrine and epinephrine in pain and emotions raises the question of the physiologic significance of these substances. Cannon thought that adrenomedullary secretion served as a reinforcing mechanism in the sympathetically innervated organs The extensive work of Celander showed, however, that the contribution of the adrenomedullary secretion to the total sympathetic effect is minimal, and subsequent work suggested that this secretion tends to inhibit sympathetic effects elicited by direct or reflex stimulation of the hypothalamus. These data support the idea that *the physiologic significance of these circulating neurohumors lies in their central, and not in their peripheral, action* Injection, as well as liberation, of norepinephrine and epinephrine resulting from the stimulation of central autonomic structures has been shown to be accompanied by excitatory and inhibitory effects on the brain. The analysis of the experimental findings seems to point out that in strictly physiologic conditions, the neurohumors tend to reduce the excitability of the posterior hypothalamus (and indirectly that of the cerebral cortex). They limit excessive hypothalamic excitability and serve thereby homeostasis via the pressoreceptor reflexes. However, the direct inhibitory action of these neurohumors on sympathetic ganglia must also be taken into consideration.

essentiality of a particular nutrient may be determined, the clinical and biochemical consequences of its deficiency assessed, and estimates of the minimum quantitative need compatible with good health obtained Probably the best-known applications of this technique have been the classical studies of Rose (1949), in which the essentiality and quantitative requirements for certain amino acids were established

It should not be assumed from the foregoing discussion that we are indebted exclusively to the human volunteer for our knowledge of any required nutrient On the contrary, countless studies with animals and bacteria have always preceded studies with the human animal, and frequently by the time the knowledge of a nutrient has progressed to the point of human experimentation, the results of an experiment can be predicted within limits

THE PROTEIN REQUIREMENT

The human requirement for exogenous protein is largely a requirement for essential *amino acids*, an essential amino acid is one that cannot be synthesized in the body at a sufficient rate to satisfy the body needs Those amino acids which have been found to be essential for man are *leucine*, *isoleucine*, *methionine*, *threonine*, *valine*, *tryptophan*, *lysine*, and *phenylalanine* In addition, certain of the essential amino acids are precursors of specific nonessential amino acids *methionine is a specific* metabolic precursor of *cystine*, *phenylalanine* is a specific metabolic precursor of tyrosine. Thus, dietary *cystine* and *tyrosine are said to* "spare" methionine and phenylalanine *in the* diet

Current knowledge concerning the complexities of amino acid requirements does not *permit* the planning of practical dietaries *on the basis* of amino acid content For *that reason*, the nitrogen requirements *of* man are most frequently considered on the basis of *protein* consumed Since the amino acid composition *of* the different types of foodstuffs varies *widely*, the minimum *amount of protein* required to maintain optimum growth and good health can only be approximated This *requirement is* greater during periods of increased growth The *protein* allowances most *recently* (1958) recommended by the National Research Council for normal adults are based on the standard of *1 Gm of protein per day per kilogram of body weight* For *pregnant* or *nursing* mothers and for growing children this allowance *is* increased (Table 2-12). These allowances assume adequate caloric intake, and it should be pointed out that the requirement for dietary protein is not enhanced by physical activity.

It is recommended that a variety of foods be included in the diet, especially those of animal origin. *Milk*, *meats*, *fish*, and *eggs* all contain protein of the highest biologic value. The *legumes* are reasonably adequate sources but are somewhat limited by their methionine content, while *cereals* are of somewhat poorer quality than the legumes and, in general, have been found to be deficient in lysine It should be remembered, however, that the proper diet is a mixed diet, and the fact that a particular foodstuff is lacking in a single nutrient does not demand its elimination from the diet. Mixtures of poor-quality protein tend to supplement each other and frequently result in a protein mixture of higher biologic value than that offered by any single component. Certain populations and religious groups have subsisted for centuries on vegetarian diets and apparently have suffered no discernible detriment to their health

THE ENERGY REQUIREMENT

Man obtains energy by oxidizing foodstuffs via complex enzymatic processes, the net energy yield being the same as if the food were combusted in a test tube. The energy requirement is, therefore, expressed in units of heat known as *calories* The calorie of metabolism is defined as the amount of heat necessary to raise the temperature of 1 kg of pure water from 15 to 16°C In general, the *Atwater factors* for the caloric yields of the major classes of foodstuffs have been adopted in America These values, which have been corrected for *digestion* losses, are 1 Gm protein yields 4 Cal, 1 Gm carbohydrate yields 4 Cal, 1 Gm fat yields 9 Cal.

The body requires energy for all body processes and activities *Specific* needs exist for (1) basal metabolism, (2) physical activity, (3) specific dynamic action of food, (4) temperature regulation, and (5) growth By making estimates of each of these needs and adding them together, the total daily requirement may be determined In practice, however, since the first two items make up the greatest part of the requirement, the last three items are usually ignored unless unusually precise estimates are needed.

Table 2-12. Food and Nutrition Board, National Research Council, Recommended Daily Dietary Allowances,* Revised, 1958

(Designed for the Maintenance of Good Nutrition of Healthy Persons in the United States)

	Age, yr	*Weight, kg (lb)*	*Height, cm (in)*	*Calories*	*Protein, Gm*	*Calcium, Gm*	*Iron, mg*	*Vitamin A, I.U*	*Thiamine, mg*	*Riboflavin, mg*	*Niacin, mg, equivalents* †	*Ascorbic acid, mg*	*Vitamin D, I.U*
Men	25	70 (154)	175 (69)	3,200 ‡	70	0.8	10	5,000	1.6	1.8	21	75	
	45	70 (154)	175 (69)	3,000	70	0.8	10	5,000	1.5	1.8	20	75	
	65	70 (154)	175 (69)	2,550	70	0.8	10	5,000	1.3	1.8	18	75	
Women	25	58 (128)	163 (64)	2,300	58	0.8	12	5,000	1.2	1.5	17	70	
	45	58 (128)	163 (64)	2,200	58	0.8	12	5,000	1.1	1.5	17	70	
	65	58 (128)	163 (64)	1,800	58	0.8	12	5,000	1.0	1.5	17	70	
	Pregnant (2d half)			+300	+20	1.5	15	6,000	1.3	2.0	+3	100	400
	Lactating (850 ml daily)			+1,000	+40	2.0	15	8,000	1.7	2.5	+2	150	400
Infants §	0–1/12												
	2/12–6/12	6 (13)	60 (24)	kg × 120	kg × 3.5 ‡	0.6	5	1,500	0.4	0.5	6	30	400
	7/12–12/12	9 (20)	70 (28)	kg × 100	kg × 3.5 ‡	0.8	7	1,500	0.5	0.8	7	30	400
Children	1–3	12 (27)	87 (34)	1,300	40	1.0	7	2,000	0.7	1.0	8	35	400
	4–6	18 (40)	109 (43)	1,700	50	1.0	8	2,500	0.9	1.3	11	50	400
	7–9	27 (60)	129 (51)	2,100	60	1.0	10	3,500	1.1	1.5	14	60	400
	10–12	36 (79)	144 (57)	2,500	70	1.2	12	4,500	1.3	1.8	17	75	400
Boys	13–15	49 (108)	163 (64)	3,100	85	1.4	15	5,000	1.6	2.1	21	90	400
	16–19	63 (139)	175 (69)	3,600	100	1.4	15	5,000	1.8	2.5	25	100	400
Girls	13–15	49 (108)	160 (63)	2,600	80	1.3	15	5,000	1.3	2.0	17	80	400
	16–19	54 (120)	162 (64)	2,400	75	1.3	15	5,000	1.2	1.9	16	80	400

* The allowance levels are intended to cover individual variations among most normal persons as they live in the United States under usual environmental stresses. The recommended allowances can be attained with a variety of common foods, providing other nutrients for which human requirements have been less well defined See text for more detailed discussion of allowances and of nutrients not tabulated

† Niacin equivalents include dietary sources of the preformed vitamin and the precursor, tryptophan. 60 mg tryptophan equals 1 mg niacin

‡ Calorie allowances apply to individuals usually engaged in moderate physical activity For office workers or others in sedentary occupations they are excessive. Adjustments must be made for variations in body size, age, physical activity, and environmental temperature.

§ The Board recognizes that human milk is the natural food for infants and feels that breast feeding is the best and desired procedure for meeting nutrient requirements in the first months of life No allowances are stated for the first month of life Breast feeding is particularly indicated during the first month when infants show handicaps in homeostasis because of different rates of maturation of digestive, excretory, and endocrine functions Recommendations as listed pertain to nutrient intake as afforded by cow's milk formulas and supplementary foods given the infant when breast feeding is terminated. Allowances are not given for protein during infancy.

dogs Although there has been no clear-cut demonstration of deficiency of essential fatty acids in man, it is reasonable to assume that they may be required, but a final resolution of this point must await more conclusive studies.

Setting an optimum level for the intake of dietary fat in the human being is most difficult, since conclusive information on this point is completely lacking Such recommendations as are available are based on estimates of the fat intake levels of various populations Numerous population differences that exist are brought about by different food habits, customs, and economic factors For example, Brandt (1943) has reported that the per capita daily fat intake in Britain was 124 Gm in 1934, or around 30 per cent of the daily caloric intake This figure is close to that recorded in America and Germany at the same time. In Japan, just prior to World War II, this same author reported that fat contributed only 6 to 10 per cent of the total calories, and Shen (1943) has estimated that Southern Chinese soldiers during World War II subsisted on rations in which only 3 per cent of the total caloric content was contributed by fat.

As economic conditions improve, the fat consumption of a population increases For example, the Food and Nutrition Board (1953) has pointed out that the average consumption of fat in the United States increased from 32 per cent of the total calories in 1909 to 40 per cent in 1952 The recommendations of this group in 1953 were that fat be included in the diet to a level of 20 to 25 per cent of total calories and that the essential fatty acids be present in the amount of at least 1 per cent of the total calories. For children (and for adults if for some reason high-caloric diets are indicated) it is suggested that 30 to 35 per cent of the total calories be supplied by fat It should be emphasized that these fat allowances are based more on food habits than on physiologic requirements

Opinion concerning the human requirement for fat is in such a state of flux that the 1958 report of the National Research Council lists no suggested levels of intake Accumulating data suggest a possible relationship between the quality and quantity of dietary fat and the development of degenerative heart disease It is to be hoped that the present controversy over the possible role of dietary fats in the etiology of degenerative heart disease will yield information that will permit more reliable recommendations to be made.

THE VITAMIN REQUIREMENT

The vitamins are organic compounds that are required in minute amounts in the diet in order to preserve health and well-being. The existence of such substances was discovered around the turn of the present century, and since then, there has been a tremendous advance in the knowledge of their structure and action. To medicine, the vitamin concept brought the realization that disease may be caused not only by the presence of a specific agent but by the lack of one as well.

The dramatic effects of the vitamins in the treatment of deficiency disease have attracted attention away from the major classes of foodstuffs, and the role of vitamins in the processes of nutrition is often exaggerated in the public mind There is no doubt that certain of these catalysts are absolutely necessary to the vital economy of the body. There is no doubt that certain vitamins cannot be manufactured in the body and must be obtained from the diet. However, the vitamins have no food value in themselves and can perform their vital functions only in a proper milieu of proteins, carbohydrates, fats, water, minerals, and oxygen. The ingestion of vitamins in excess of body needs is not normally beneficial, and in some cases may be actually harmful. It is to be hoped that recent advances in the knowledge of carbohydrates, fats, and protein, and a renewed cognizance of their importance in the diet may help establish a more balanced concept of nutrition

There are some half a dozen known vitamins for which clear-cut deficiencies have been observed in man and about which sufficient knowledge is available to permit the recommendation of desirable daily levels of intake. These are *vitamins A, C, D, thiamine, riboflavin, and niacin* Vitamins for which deficiencies have been observed in nature but which do not meet the latter qualification are *vitamins K,* B_6, B_{12}, *and folic acid* Other known vitamins that are probably dietary essentials for man are *pantothenic acid, biotin, and vitamin E* Whether or not *choline, inositol,* and *p-aminobenzoic acid* should be considered vitamins is a moot question

Recommended daily caloric allowances for populations have been published by the *Food and Agricultural Organization of the United Nations* (1957). For the "reference" man and woman at rest the FAO caloric recommendation is 92 $(W_{kg})^{0.73}$ and 82.5 $(W_{kg})^{0.73}$, respectively. Additional amounts are added or subtracted to adjust for age, activity, environmental temperature, physiologic state, etc. These standards have been employed as the basis for the caloric recommendations of the Food and Nutrition Board of the National Research Council (1958). These allowances for various age groups are seen in Table 2-12

Various adjustments are suggested. A reduction *of 3 per cent in total caloric allowance per decade* between the ages of 30 and 50 and a 7.5 per cent decrease per decade between the ages of 50 and 70 *is recommended A further decrement of* 10 per cent is recommended for the years 70 to 80. It is recommended that a 5 per cent increase be made for the first 10° decrease from the standard environmental temperature of 20°C, and a 3 per cent increase for each additional 10° decrease In the same way, allowances should be *reduced* 5 per cent for each 10° increase above the standard temperature It is suggested that the following formulas be used for estimating the caloric allowances of persons whose weight and height differ from those of the reference men and women cited in Table 2-12

Daily caloric allowance for men 0 95(815 + 36 6W)

Daily caloric allowance for women. 0 95(580 + 31 1W)

where W is the desirable body weight in *kilograms* Desirable body weights for height are shown in Table 2-13

TABLE 2-13 DESIRABLE WEIGHTS FOR HEIGHT

Height, in	*Weight, lb*	
	Men	*Women*
58		112 ± 11
60	125 ± 13	116 ± 12
62	130 ± 13	121 ± 12
64	135 ± 14	128 ± 13
66	142 ± 14	135 ± 14
68	150 ± 15	142 ± 14
70	158 ± 16	150 ± 15
72	167 ± 17	158 ± 16
74	178 ± 18	

SOURCE: Modified from *Metropolitan Life Insurance Company Statistical Bulletin* 23, 1942; 24, 1943. Age is disregarded because weight gains beyond the ages of 25 to 30 years are considered undesirable

Other conditions that have to be considered in determining caloric allowances are pregnancy, lactation, rapid growth, degree of physical activity, and metabolic anomalies Obviously, so many factors must be considered in predicting caloric needs that, even at their best, such predictions can be only crude approximations.

CARBOHYDRATE

Carbohydrate is the cheapest and, therefore, the most common source of calories in the diet However, it should be pointed out that there is no specific need for dietary carbohydrate in the sense that certain amino acids or vitamins are essential—there are no known "essential" sugars Since calories may also be obtained from proteins or fats, dietary carbohydrate is completely dispensable, but it is difficult to design an acceptable and economical diet that does not contain a reasonable proportion of carbohydrate calories In the United States, for example, carbohydrates provide from 50 to 60 per cent of dietary calories; in other coun*tries they may provide as much as* 80 per cent. Since certain carbohydrate-rich foods are quite inexpensive, the lower economic levels of a population have a greater *proportion of* carbohydrate in the diet than do the higher-income groups. Highly refined grain products and sugars are usually the cheapest source of calories available, but diets containing too high a proportion of these items are likely to be poor in certain essential amino acids, minerals, and vitamins. No recommended intake of carbohydrate is suggested by the National Research Council

THE FAT REQUIREMENT

Fat has the highest caloric value of any of the major foodstuffs, yielding 9 Cal/Gm as contrasted to 4 Cal/Gm for both carbohydrate and protein In addition to its caloric function, fat adds much to the palatability and satiety *of a diet.*

As far as is now known, the absolute requirement for dietary fat by man is probably limited *to trace quantities of* certain unsaturated fatty acids These "essential" fatty acids are *linoleic* and *linolenic*, which are found in vegetable oils, *and arachidonic, which occurs* exclusively in animal fats When these acids are absent from the diet of young rats, they cease to grow after 2 to 3 *months and develop an* eczematous condition of the skin and feet and a "scaly" tail Similar conditions have been demonstrated in

cellular substances, and in its absence, the symptoms of *scurvy* occur.

According to the British Medical Research Council (1946) a *daily ascorbic acid intake of 10 mg* may be expected to prevent scurvy for 1 year and maintain good healing properties of the tissues [illegible]

recommended *an intake of 30 mg daily*, a level also suggested by the Canadian Council on Nutrition *(1950)*.

The National Research Council considers that a more liberal allowance is desirable and has recommended *an intake of 70 to 75 mg daily* for the average adult American. The specific recommendations of this group are shown in Table 2-12.

The best dietary sources of ascorbic acid are fruits (particularly of the citrus variety) and vegetables The only animal source of this vitamin that might be termed adequate is liver Under the usual conditions of consumption, meats, cereals, and dairy products are poor sources of ascorbic acid

Thiamine The requirement for thiamine is closely geared to the carbohydrate intake, since diphosphothiamine (cocarboxylase) functions as a coenzyme in the metabolism of *pyruvic acid*, which is an intermediate in carbohydrate metabolism. A deficiency of this vitamin results in the clinical entity known as *beriberi*, which is characterized by degenerative changes in the nervous system However, this syndrome is frequently complicated by coexisting deficiencies of other of the B vitamins

Although protein and fat may also contribute calories to the diet, it is customary to consider the thiamine requirement in terms of the total calories in the diet. There have been many studies of the *minimum* thiamine requirement for adults, the figures usually quoted fall in the *range from 0.13 to 0 50 mg/1000 Cal* The estimates for infants (0.14 to 0 20 mg) as reported by *Holt et al (1949)* are of the same magnitude, but there is a lack of satisfactory data on older children

The current National Research Council recommendations (Table 2-12) exceed these figures, since a daily allowance should be sufficient not only to prevent signs of clinical or biochemical deficiency but to maintain body stores as well The best food sources of thiamine are yeast, liver, pork, cow's milk, eggs, and fresh green vegetables. Although whole cereals may be good sources of this nutrient, much is lost in milling and processing and, as a result, processed cereals, nonenriched flours, and rice are poor sources of thiamine.

Riboflavin. Riboflavin exists in a phosphorylated form as a component of several flavoprotein enzymes which participate in cellular oxidation In particular, these enzymes are believed to be largely responsible for respiration in the cornea, which has a poorly developed vascular system.

The exact characteristics of riboflavin deficiency in man are still not agreed upon by nutrition authorities.

The magnitude of the human requirement for riboflavin has not been definitely established, but since changes in nitrogen balance markedly change the urinary excretion of this vitamin, *the riboflavin requirement seems to be related to protein metabolism*. For this reason, the National Research Council (1958) suggests that the daily riboflavin allowance may be calculated from the recommended protein allowance by multiplying by the factor 0.025. The daily requirements so estimated can be seen in Table 2-12.

Dairy foods and other animal protein sources supply riboflavin in the greatest amounts in the diet. Green leaves of plants and yeast are also particularly rich in this vitamin.

Niacin (Nicotinic Acid). Niacin, or nicotinic acid, is β-pyridine carboxylic acid The amide of this compound is also active and occurs in the body primarily as a component of certain coenzymes that are involved in respiration and glycolysis

In recognition of the tryptophan-niacin conversion, the presently recommended allowance of the National Research Council (1958) (Table 2-12) is presented in terms of "niacin equivalents," in which it is estimated that 60 mg tryptophan is equivalent to 1 mg niacin At present no tables are available rating foodstuffs in terms of niacin equivalents, but it is probable that such tables will soon be forthcoming. The richest sources of niacin are peanuts, liver, and yeast Muscle meats are generally low in niacin, and most fruits, vegetables, milk, and eggs are poor sources There is not a great deal of variation in the tryptophan content of various foodstuffs, but those of animal origin are somewhat better sources of this amino acid.

Pellagra, the result of niacin deficiency in man, has been endemic for hundreds of years in areas where corn is the main item in the diet. Clinically, it is characterized by the three D's—dermatitis, diarrhea, and dementia.

Estimates of the human requirement for niacin are complicated because the amino acid tryptophan may serve as a precursor. In fact, tryptophan alone can heal the lesions of the pellagrin (Bean et al., 1951), and it has become evident during the past few years that the role played by corn in the etiology of pellagra is not so simple as once believed Not only is corn low in tryptophan, but it would appear that the niacin which is present is not completely available to the pig (Kodicek et al., 1956) or the rat (Pearson et al., 1957).

Vitamin A. An adequate intake of vitamin A or its carotenoid precursors is essential to growth, to the integrity of the epithelial tissues, and to vision. Although considerable progress has been made in establishing the importance of vitamin A in the latter function, it should be pointed out that its principal activity is in *growth.* As Wald (1953) so aptly puts it, "It is enough to recall that animals deprived of vitamin A stop growing and eventually die and neither as the result of night-blindness."

The absorption and utilization of vitamin A and the carotenes depend upon a number of factors such as the extent of liver storage, the form in which the vitamin A is ingested, and the presence of fat in the intestine. In general, carotene is absorbed much less readily than is the preformed vitamin A.

A well-controlled study of vitamin A deficiency in the human being was carried on in Great Britain during World War II by Hume and Krebs (1949). The data compiled in this study led the investigators to suggest that a daily dose of 1,300 International Units (I.U) was sufficient to cure a deficiency and that 2,500 I.U constituted a margin of safety *The minimum protective dose of carotene was estimated to be about 1,500 I U daily.* However, since this precursor is not so well absorbed as vitamin A itself, it was recommended that the daily intake be about *7,500 I U.*

The latest recommendations of the Food and Nutrition Board are shown in Table 2-12 In general, a daily allowance of 5,000 to 6,000 I U of vitamin A is suggested as a practical goal for adults, with somewhat reduced daily allowances for various age groups of children.

The carotenoid precursors of vitamin A are found in abundant quantity in dark green and yellow *vegetables and yellow fruits. Eggs, milk, and liver* contain relatively large quantities of the preformed vitamin and less of the carotenoid precursors

Vitamin D. Although there are about 10 structurally similar compounds that possess vitamin D activity, the most important precursors are *ergosterol,* the main source of which is yeast, and *7-dehydrocholesterol,* which is of animal origin and is present in the skin Under the influence of ultraviolet irradiation, these substances produce *vitamins* D_2 *and* D_3, respectively. A deficiency of vitamin D or its precursors in the diet results in a disturbance of bone development in infancy and childhood known as rickets Like vitamin A and the other fat-soluble vitamins, this vitamin is stored in good quantities in the liver, which probably accounts for the fact that vitamin D deficiency (osteomalacia) is rarely seen in the adult.

There is a considerable body of literature concerning the vitamin D requirement of the infant, but little information on the requirement of the adult is available. Jeans and Stearns (1938) found that from 300 to 400 I.U. daily permits maximum calcium retention in the infant and that this is associated with excellent skeletal growth and early dentition. The same investigators (1951) presented evidence that the need for vitamin D in adolescence is as great as in infancy

The vitamin D requirement of the average adult seems to be very low because exposure to the sun normally manufactures large quantities in the skin Accordingly, the Food and Nutrition Board concludes that "the need for supplemental vitamin D of vigorous adults leading a normal life seems to be minimum. For persons working at night and for nuns and others whose habits shield them from the sunlight, as well as for elderly persons, the ingestion of small amounts of vitamin D is desirable." Although during pregnancy and lactation the requirements for calcium and phosphorus are increased, it would appear that the usual intake of vitamin D is sufficient to promote adequate utilization of these elements. The allowances of the National Research Council (1958) are shown in Table 2-12.

The best natural food sources of vitamin D are of animal origin—the livers of certain species of fish such as the tuna, swordfish, and cod being particularly potent sources In addition, milk, butter, and eggs are reasonable sources of this vitamin It is virtually absent from the tissues of higher plants.

Vitamin K. Vitamin K is essential for the synthesis of prothrombin and for normal blood clotting The most common form in therapeutic use is a synthetic analogue known as *menadione,* which is several times more active than the naturally occurring forms.

In the adult, the bacterial flora of the intestine will usually provide an adequate amount of vitamin K, but the newborn child cannot depend upon a supply from this source until the third or fourth day of life. For this reason the newborn infant may have hypoprothrombinemia, and pregnant women are frequently given a daily oral dose of 1 mg menadione during the last month of pregnancy Usually the child will also be given a single 1-mg dose parenterally at birth to cover his needs until the bacterial flora develop

The vitamin K requirement of healthy adults has been estimated to be around 1 mg daily, and this is probably met by bacterial synthesis Additional quantities may be obtained from a variety of foodstuffs Green vegetables such as spinach and cabbage are particularly good sources, and, in general, the vitamin is widely distributed in nature

Vitamin C. Ascorbic acid is the vitamin designated as vitamin C or as *the antiscorbutic factor.* It is required for the proper formation of inter-

cellular substances, and in its absence, the symptoms of *scurvy* occur

According to the British Medical Research Council (1946) *a daily ascorbic acid intake of 10 mg* may be expected to prevent scurvy for 1 year and maintain good healing properties of the tissues. However, it is doubtful if optimum ascorbic acid nutriture is maintained at this low level of intake. To allow for a margin of safety this organization recommended *an intake of 30 mg daily*, a level also suggested by the Canadian Council on Nutrition (1950).

The National Research Council considers that a more liberal allowance is desirable and has recommended *an intake of 70 to 75 mg daily* for the average adult American The specific recommendations of this group are shown in Table 2-12.

The best dietary sources of ascorbic acid are fruits (particularly of the citrus variety) and vegetables The only animal source of this vitamin that might be termed adequate is liver Under the usual conditions of consumption, meats, cereals, and dairy products are poor sources of ascorbic acid

Thiamine The requirement for thiamine is closely geared to the carbohydrate intake, since diphosphothiamine (cocarboxylase) functions as a coenzyme in the metabolism of pyruvic acid, which is an intermediate in carbohydrate metabolism. A deficiency of this vitamin results in the clinical entity known as *beriberi*, which is characterized by degenerative changes in the nervous system However, this syndrome is frequently complicated by coexisting deficiencies of other of the B vitamins

Although protein and fat may also contribute calories to the diet, it is customary to consider the thiamine requirement in terms of the total calories in the diet There have been many studies of the minimum thiamine requirement for adults, the figures usually quoted fall in the range from 0.13 to 0.50 mg/1000 Cal The estimates for infants (0.14 to 0.20 mg) as reported by *Holt et al.* (1949) are of the same magnitude, but there is a lack of satisfactory data on older children

The current National Research Council recommendations (Table 2-12) exceed these figures, since a daily allowance should be sufficient not only to prevent signs of clinical or biochemical deficiency but to maintain body stores as well. The best food sources of thiamine are yeast, liver, pork, cow's milk, eggs, and fresh green vegetables. Although whole cereals may be good sources of this nutrient ... and, as a ... flours, and ...

Riboflav... form as a ... flavoprotein enzymes which participate in cellular oxidation. In particular, these enzymes are believed to be largely responsible for respiration in the cornea, which has a poorly developed vascular system

The exact characteristics of riboflavin deficiency in man are still not agreed upon by nutrition authorities

The magnitude of the human requirement for riboflavin has not been definitely established, but since changes in nitrogen balance markedly change the urinary excretion of this vitamin, *the riboflavin requirement seems to be related to protein metabolism.* For this reason, the National Research Council (1958) suggests that the daily riboflavin allowance may be calculated from the recommended protein allowance by multiplying by the factor 0 025. The daily requirements so estimated can be seen in Table 2-12

Dairy foods and other animal protein sources supply riboflavin in the greatest amounts in the diet. Green leaves of plants and yeast are also particularly rich in this vitamin.

Niacin (Nicotinic Acid). Niacin, or nicotinic acid, is β-pyridine carboxylic acid. The amide of this compound is also active and occurs in the body primarily as a component of certain coenzymes that are involved in respiration and glycolysis.

In recognition of the tryptophan-niacin conversion, the presently recommended allowance of the National Research Council (1958) (Table 2-12) is presented in terms of "niacin equivalents," in which it is estimated that 60 mg tryptophan is equivalent to 1 mg niacin At present no tables are available rating foodstuffs in terms of niacin equivalents, but it is probable that such tables will soon be forthcoming. The richest sources of niacin are peanuts, liver, and yeast. Muscle meats are generally low in niacin, and most fruits, vegetables, milk, and eggs are poor sources There is not a great deal of variation in the tryptophan content of various foodstuffs, but those of animal origin are somewhat better sources of this amino acid

Pellagra, the result of niacin deficiency in man, has been endemic for hundreds of years in areas where corn is the main item in the diet. Clinically, it is characterized by the three D's—dermatitis, diarrhea, and dementia.

Estimates of the human requirement for niacin are complicated because the amino acid tryptophan may serve as a precursor In fact, tryptophan alone can heal the lesions of the pellagrin (Bean et al, 1951), and it has become evident during the past few years that the role played by corn in the etiology of pellagra is not so simple as once believed Not only is corn low in tryptophan, but it would appear that the niacin which is present is not completely available to the pig (Kodicek et al, 1956) or the rat (Pearson et al, 1957).

Evidence suggesting that there may be a pellagragenic factor in this cereal (Woolley, 1946) remains unconfirmed.

Until more is known about the amino acid content of diets and the magnitude of the tryptophan-niacin conversion in man, it would appear that the presently recommended allowances of the National Research Council (1958) are ample. The richest sources of niacin are peanuts, liver, and yeast. Muscle meats are generally low, and most fruits, vegetables, milk, and eggs are poor sources.

Vitamin B_{12}. Vitamin B_{12} is a red, cobalt-containing crystalline compound, of molecular weight 1,500, whose structure has recently been elucidated. In general, the molecule resembles a porphyrin with the cobalt linked coordinately in much the same way as is the iron in heme Knowledge of its physiologic action is incomplete, but it is known to be involved in the metabolic transfer of one-carbon fragments and in the synthesis and breakdown of nucleic acids.

Although *pernicious anemia* is the result of a vitamin B_{12} deficiency, this disease is brought about by the lack of an "intrinsic factor" in the gastric secretions, rather than by the absence of the vitamin from the diet. The role of the "intrinsic factor" in the metabolism of vitamin B_{12} is unknown There is no clear-cut syndrome in nature that has been conclusively demonstrated to be caused by the dietary lack of vitamin B_{12} alone. Combined dietary deficiencies of vitamin B_{12} and folic acid may result in what is known as *nutritional macrocytic anemia*. The hemogram in this disease resembles that of pernicious anemia, but the achlorhydria and the neurologic manifestations that are typical of pernicious anemia are lacking

It has been well established that as little as *1 μg of parenteral B_{12} daily* will maintain the pernicious anemia patient in remission, but one cannot legitimately use this figure in predicting the requirements of a healthy population In recognition of this fact, the National Research Council has made no recommendation as to the dietary need for vitamin B_{12}

The current microbiologic techniques employed for the assay of this vitamin are rather nonspecific, and the estimates of the vitamin B_{12} content of foodstuffs are not very accurate However, it may be said that the best dietary sources of vitamin B_{12} are liver, kidney, meat, and milk Virtually no vitamin B_{12} is found in the higher plants

The Folic Acid Group. The folic acid group consists of a number of closely related *pteridine derivatives*. A number of glutamic acid conjugates of folic acid probably occur in nature, but only the triglutamate and heptaglutamate have been isolated The 5-formyl derivative (folinic acid or citrovorum factor) and the 10-formyl derivative have been isolated, and these may also occur in the form of glutamic acid conjugates

Folinic acid participates in the transfer of single carbon units—the formyl group probably being itself transferred. In particular, it is involved in the synthesis of desoxyribonucleic acid and in hemoglobin formation. A deficiency of members of this group results in anemia, leukopenia, diarrhea, and gastrointestinal lesions in the monkey (Day et al, 1938). Identical symptoms have not been produced by dietary deficiency in man, but it is pertinent that those diseases which respond to therapy with members of the group are characterized by similar defects in hematopoiesis and gastrointestinal physiology. Accordingly, folic acid or its derivatives have been used with varying degrees of effectiveness in the treatment of pernicious anemia, sprue, infantile megaloblastic anemia, and "pernicious anemia" of pregnancy.

Sufficient data are not available to permit the setting of a minimum or optimum requirement of folic acid Since the average daily diet will contain *from 0 5 to 1 0 mg*, it is probable that this amount will maintain adequate health under most conditions. Liver is by far the best-known source, and green vegetables contain fair quantities Milk and fruits contribute little or no folic acid to the diet

The Vitamin B_6 Group. This group consists of pyridoxine, pyridoxamine, pyridoxal, and pyridoxal phosphate. Pyridoxal phosphate functions as a coenzyme for transaminations, deaminations, desulfurations, and decarboxylations It is also involved in the conversion of tryptophan to niacin, and in vitamin B_6 deficiency, a test dose of tryptophan will cause the increased excretion of xanthurenic acid, a product of tryptophan metabolism.

Vilter et al (1953) have produced *experimental vitamin B_6 deficiency in the human* being by feeding the antagonist, 4-desoxypyridoxine. Deficiency of this vitamin has been produced in infants fed a purified diet devoid of vitamin B_6 (Snyderman et al, 1950), and it has also been reported as occurring in infants fed from birth on a commercial liquid milk formula In these cases, the deficiency was characterized by growth arrest and convulsions

Only a rough estimate of the human B_6 requirement can be made Vilter (1953) has estimated it to be approximately *1 5 mg/day* Diet analyses suggest that this amount may be readily obtained from the average diet.

Other Vitamins. Only crude estimates can be made of the daily dietary requirements for the other vitamins presumed to be dietary essentials for man These are *biotin*, 150 to 300 μg, *pantothenic acid*, 10 mg, *choline*, 150 to 250 mg, and *vitamin E*, 7 mg No satisfactory figure for *inositol* can be stated at this time Diets that are known

to be adequate in all other respects are not likely to be deficient in these nutrients

INORGANIC NUTRIENTS

Man requires the presence of certain inorganic substances in his diet. These may serve structural functions or as necessary components of enzyme systems.

Those minerals considered to be of first importance are *calcium, phosphorus, iron, iodine, sodium, potassium, copper,* and *fluorine.* Sufficient knowledge is available concerning these substances to permit reasonable intake recommendations to be made, and either the clinical signs of deficiencies or the beneficial effects of their ingestion have been seen in the human being.

Calcium and Phosphorus. Calcium and phosphorus make up the major part of the mineral content of the bones and teeth About 99 per cent of body calcium is found in the skeletal tissues, and skeletal phosphorus comprises about 70 to 80 per cent of the body stores In addition to its structural function, calcium is required *in the clotting of blood* and has also been shown to activate certain enzymes. Phosphorus is a component of phospholipids, and phosphorylation and dephos[illegible] down

Th[illegible] gastrointestinal tract is mediated directly by vitamin D However, a host of other factors have been shown to be involved, among these being the previous dietary intake of calcium, the protein and calcium content of the diet, the presence of substances which form insoluble precipitates with calcium in the gut (phytic acid of cereals, oxalic acid of certain vegetables), and the pH of the intestinal contents

The numerous factors that influence calcium absorption make it difficult to predict accurately the daily requirement As might be expected, the growing child has a high calcium requirement during the first year of life After the first year, the requirement drops off somewhat until the increased demands brought on by the growth spurt of puberty The well-nourished adult has only to maintain his calcium stores—i e, remain in calcium balance In general, most adults are found to be in balance at the level of intake supplied by their usual diet whether it be high or low Calcium requirements in women are increased during pregnancy and lactation

The recommended allowances proposed by the National Research Council (1958) are detailed in Table 2-12 Such intakes may be easily attained if reasonable quantities of milk, milk products, and green leafy vegetables are consumed

Most human diets contain adequate quantities of phosphorus The Food and Nutrition Board (1953) concludes that "the phosphorus allowances should be at least equal to those for calcium in the diets of children and of women during the latter part of pregnancy and during lactation. For other adults the phosphorus allowances should be approximately one and one half times those for calcium In general, it is safe to assume that if the calcium and protein needs are met through common foods, the phosphorus requirement also will be covered, because the common foods richest in calcium and protein are also the best sources of phosphorus"

Iron. Iron is an important part of the heme proteins, the best known of which are hemoglobin and myoglobin Iron also occurs in the heme-containing cellular oxidation catalysts such as the cytochromes, cytochrome oxidase, and peroxidase It also forms an integral part of the catalase molecule which catalyzes the decomposition of hydrogen peroxide

Iron deficiency may be of either a primary (dietary) or a secondary (conditioned) origin. In both instances it is usually reflected by a *hypochromic microcytic anemia* Dietary deficiency is a common cause of iron deficiency anemia in the infant and may also be implicated occasionally in the young adolescent In the adult, however, iron deficiency is nearly always the result of blood loss. Such blood losses may result from excessive menstrual bleeding, chronic bleeding of hemorrhoids, peptic ulcers, repeated epistaxis, or hookworm infestation

Numerous estimates of the iron requirement of man have been made In general, it has been found that the adult male can be maintained for long periods of time on very low intakes of iron. The studies of Moore and Dubach (1951) have shown that the absorption of radioactive iron from foodstuffs by adults is relatively inefficient, *only about 10 per cent being absorbed.* Since these workers also estimate that the normal adult male must absorb 0 5 to 1 0 *mg* iron per day for balance while the normal adult woman must absorb 1 0 to 1 5 mg/day for balance, it can be seen that *10 to 15 mg of daily dietary iron is necessary to maintain balance*

The most recent National Research Council Report (1958) sets the daily iron requirement for infants at about 0 8 mg/kg body weight, for the preschool child at 0 3 to 0 4 mg/kg body weight, and the requirement of children from 7 to 11 years at 0 35 mg/kg body weight The recommended allowances for adults and children would appear to be liberal (Table 2-12).

Evidence suggesting that there may be a pellagragenic factor in this cereal (Woolley, 1946) remains unconfirmed.

Until more is known about the amino acid content of diets and the magnitude of the tryptophan-niacin conversion in man, it would appear that the presently recommended allowances of the National Research Council (1958) are ample. The richest sources of niacin are peanuts, liver, and yeast. Muscle meats are generally low, and most fruits, vegetables, milk, and eggs are poor sources.

Vitamin B_{12}. Vitamin B_{12} is a red, cobalt-containing crystalline compound, of molecular weight 1,500, whose structure has recently been elucidated. In general, the molecule resembles a porphyrin with the cobalt linked coordinately in much the same way as is the iron in heme. Knowledge of its physiologic action is incomplete, but it is known to be involved in the metabolic transfer of one-carbon fragments and in the synthesis and breakdown of nucleic acids.

Although *pernicious anemia* is the result of a vitamin B_{12} deficiency, this disease is brought about by the lack of an "intrinsic factor" in the gastric secretions, rather than by the absence of the vitamin from the diet. The role of the "intrinsic factor" in the metabolism of vitamin B_{12} is unknown. There is no clear-cut syndrome in nature that has been conclusively demonstrated to be caused by the dietary lack of vitamin B_{12} alone. Combined dietary deficiencies of vitamin B_{12} and folic acid may result in what is known as *nutritional macrocytic anemia*. The hemogram in this disease resembles that of pernicious anemia, but the achlorhydria and the neurologic manifestations that are typical of pernicious anemia are lacking.

It has been well established that as little as *1 μg of parenteral B_{12} daily* will maintain the pernicious anemia patient in remission, but one cannot legitimately use this figure in predicting the requirements of a healthy population. In recognition of this fact, the National Research Council has made no recommendation as to the dietary need for vitamin B_{12}.

The current microbiologic techniques employed for the assay of this vitamin are rather nonspecific, and the estimates of the vitamin B_{12} content of foodstuffs are not very accurate. However, it may be said that the best dietary sources of vitamin B_{12} are liver, kidney, meat, and milk. Virtually no vitamin B_{12} is found in the higher plants.

The Folic Acid Group. The folic acid group consists of a number of closely related *pteridine derivatives*. A number of glutamic acid conjugates of folic acid probably occur in nature, but only the triglutamate and heptaglutamate have been isolated. The 5-formyl derivative (folinic acid or citrovorum factor) and the 10-formyl derivative have been isolated, and these may also occur in the form of glutamic acid conjugates.

Folinic acid participates in the transfer of single carbon units—the formyl group probably being itself transferred. In particular, it is involved in the synthesis of desoxyribonucleic acid and in hemoglobin formation. A deficiency of members of this group results in anemia, leukopenia, diarrhea, and gastrointestinal lesions in the monkey (Day et al, 1938). Identical symptoms have not been produced by dietary deficiency in man, but it is pertinent that those diseases which respond to therapy with members of the group are characterized by similar defects in hematopoiesis and gastrointestinal physiology. Accordingly, folic acid or its derivatives have been used with varying degrees of effectiveness in the treatment of pernicious anemia, sprue, infantile megaloblastic anemia, and "pernicious anemia" of pregnancy.

Sufficient data are not available to permit the setting of a minimum or optimum requirement of folic acid. Since the average daily diet will contain *from 0.5 to 1.0 mg*, it is probable that this amount will maintain adequate health under most conditions. Liver is by far the best-known source, and green vegetables contain fair quantities. Milk and fruits contribute little or no folic acid to the diet.

The Vitamin B_6 Group. This group consists of pyridoxine, pyridoxamine, pyridoxal, and pyridoxal phosphate. Pyridoxal phosphate functions as a coenzyme for transaminations, deaminations, desulfurations, and decarboxylations. It is also involved in the conversion of tryptophan to niacin, and in vitamin B_6 deficiency, a test dose of tryptophan will cause the increased excretion of xanthurenic acid, a product of tryptophan metabolism.

Vilter et al (1953) have produced experimental vitamin B_6 deficiency in the human being by feeding the antagonist, 4-desoxypyridoxine. Deficiency of this vitamin has been produced in infants fed a purified diet devoid of vitamin B_6 (Snyderman et al, 1950), and it has also been reported as occurring in infants fed from birth on a commercial liquid milk formula. In these cases, the deficiency was characterized by growth arrest and convulsions.

Only a rough estimate of the human B_6 requirement can be made. Vilter (1953) has estimated it to be approximately *1.5 mg/day*. Diet analyses suggest that this amount may be readily obtained from the average diet.

Other Vitamins. Only crude estimates can be made of the daily dietary requirements for the other vitamins presumed to be dietary essentials for man. These are *biotin*, 150 to 300 μg, *pantothenic acid*, 10 mg; *choline*, 150 to 250 mg, and *vitamin E*, 7 mg. No satisfactory figure for *inositol* can be stated at this time. Diets that are known

TABLE 2-14. THE BASIC SEVEN FOOD GROUPS (*cont*)

Group	*Recommended no of servings per day*	*Foods*	
Group V. Meat, poultry, fish, eggs, dried peas, beans, nuts	2 or more	Beef	Chicken
		Lamb	Duck
		Veal	Turkey
		Pork	Goose
		Rabbit	
		Organ and variety meats:	
		Liver	
		Heart	
		Tongue and all other edible organs	
		Sausage, luncheon meats	
		Fish and seafood	
		All edible wild game	
		Eggs	
		Dried beans and peas—all varieties	
		Lentils	
		Soybeans	
		Nuts—including butters and spreads	
Group VI: Bread, flour, cereals (whole-grain, enriched, or restored)	Daily	Whole grain:	
		Oatmeal	
		Cornmeal	
		Whole-wheat flour	
		Rye	
		Other cereals and starches:	
		Breads	Spaghetti
		Breakfast foods	Crackers
		Macaroni	Rice
		Noodles	
		Thickening agents:	
		Cornstarch	
		Tapioca	
Group VII Butter and fortified margarine	Daily	Butter	
		Oleomargarine (colored or uncolored—if *fortified)*	
Additional foods	Enough daily to supply caloric value and to make meals palatable and satisfying	Sugar:	Honey
		Brown	*Molasses*
		White	Jellies, jams, and marmalades
			Desserts

but usually most of the daily intake *is supplied* by drinking water The average adult ingests from [illegible]

elements are *essential* nutrients, but their distribution in common foodstuffs is so ubiquitous that dietary *deficiencies are seldom* seen Conditioned deficiencies of sodium *and chloride* appear most frequently as the result of adrenocortical insufficiency, or because of extensive losses through vomiting, diarrhea, or *sweating*. Potassium deficiency may occur under similar circumstances

The sodium chloride *intake* of the average adult has been estimated to be from *7 to 15 Gm daily.* This amount includes both that normally *present* in the diet and that added as seasoning. *Conditions that* produce profuse sweating increase the requirement, and *additional salt* must be consumed to maintain electrolyte balance An exact allowance for *sodium chloride* cannot be set, but the normal requirements are *easily met by* a typical mixed diet

Iodine. Iodine is an essential element for man and functions *principally* in formation of the thyroid hormone. In geographic regions characterized by a *low iodine* intake, the usual deficiency found is simple goiter, in areas of *extremely* poor

The available iron in foods may vary from 15 to 90 per cent. In general the best dietary sources are liver and other meats, eggs, legumes, leafy green vegetables, and whole-grain or enriched cereals.

Fluorine. Fluorine is found in trace amounts in animal tissues, particularly in the skeletal system, but no definite statement concerning its essentiality for man can be made. A deficiency of this element in experimental animals has never been produced, probably because of the difficulty in devising a diet that is completely fluoride-free.

Overwhelming epidemiologic evidence indicates that fluorine plays a vital role in the development of the tooth, and it is now widely recognized that the ingestion of drinking water containing about 1 ppm of fluoride during tooth development results in a substantial decrease in dental caries. As a result, the fluoridation of public water supplies has now become a widespread practice, and the American Public Health Association and the American Dental Association have passed resolutions supporting this program.

Seafoods are particularly good sources of fluorine,

TABLE 2-11 THE BASIC SEVEN FOOD GROUPS

Group	*Recommended no. of servings per day*	*Foods*	
Group I: Green leafy and yellow vegetables	1 or more	Green leafy: Asparagus Broccoli Beet tops Brussels sprouts Green beans Chard Spinach Endive Dandelion greens Lettuce Peas Watercress	Yellow: Carrots Sweet potatoes Rutabagas Yellow turnips Squash
Group II Citrus fruits, tomatoes, raw cabbage	1 or more	Oranges Orange juice Grapefruit Grapefruit juice Tomatoes	Tomato juice Tangerines Tangerine juice Blended juices Raw cabbage
Group III: Potatoes and other vegetables and fruits	2 or more	Potatoes Beets Cauliflower Celery Eggplant Lima beans Onions Parsnips Radishes Turnips Wax beans Rhubarb	Apples Bananas Berries Cherries Peaches Pears Pineapple Fresh or dried fruits Apricots Dates Figs Prunes Raisins
Group IV Milk, cheese, ice cream	Children—3–4 cups Adults—2 or more cups	Milk: Fresh whole Fresh skimmed Evaporated Dried whole Dried skimmed Buttermilk	Cheese—all kinds Ice cream Milk sherbets

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Increased capillary permeability

W. C. SPECTOR

For present purposes, *capillaries* will be defined as blood vessels whose wall is formed essentially only by vascular endothelium, the term therefore including both true capillaries and venules. An alteration in the properties of the walls of such vessels is responsible for the exudation of plasma protein and blood cells into the injured tissues, as in inflammation [1] These endothelium-lined tubes are freely permeable to water and salts but only slightly permeable to plasma proteins and similar colloids. With severe physical damage, the walls of these vessels may be destroyed, with resultant perivascular hemorrhage. With lesser degrees of injury, such as those responsible for acute inflammation in infections, burns, trauma, and local hypergic antigen-antibody reactions, the wall undergoes an increased permeability to plasma protein This inability to retain plasma proteins is termed "increased capillary permeability", this is the meaning of the term in the present context. However, some space will be devoted to the associated, but probably separate, phenomenon of increased permeability to blood leucocytes, commonly termed "leucocyte emigration"

DEMONSTRATION OF INCREASED CAPILLARY PERMEABILITY

Clinically, increased capillary permeability is manifest as *edema*, i e , the abnormal collection of fluid in the tissues Such edema may be visible, as in infection, burning, or trauma of the skin or subcutaneous tissues, or it may be occult and demonstrable only as an increase in weight or in water content. It is important to realize that not every edema is due to increased capillary permeability Thus, in edema due to uncomplicated heart failure or nephrotic syndrome, the fault lies in *increased hydrostatic pressure or reduced oncotic pressure in the vessels, or in sodium retention by the extravascular tissues* There are in fact two main types of edema *inflammatory*, due to increased capillary permeability to protein, and *noninflammatory*, in which capillary permeability to protein is normal and the abnormal amount of fluid in the tissues is due to causes other than changes in the capillary wall. The two varieties are sharply distinguished by the protein content of the edema fluid, which is high in the inflammatory type and low in the other. This difference may be illustrated in cases of the nephrotic syndrome with ascites due to hypoproteinemia and sodium retention The ascitic fluid of such patients will have a protein content of 10 mg/100 ml or less However, should peritonitis supervene, as it may in nephrotic children, the protein content of the ascitic fluid would rise to as much as 4,000 mg/100 ml.

EXPERIMENTAL DEMONSTRATION OF INCREASED CAPILLARY PERMEABILITY

To study the phenomenon experimentally, it is necessary to follow the time course of increased capillary permeability to protein and

[1] See also Chap. 18 Editor.

intake both hypothyroidism and cretinism may be found.

The iodine requirement for man has been estimated to be between 0.10 and 0.20 mg/day (Greer, 1955). The Food and Nutrition Board (1958) states that an ample allowance for the adult is from 0 15 to 0 30 mg daily and suggests that this may be met by the regular use of iodized salt. It is especially important that iodized salt be used during adolescence and pregnancy since the need for iodine is apparently increased during these periods of physiologic stress. Since iodized salt in the United States contains 0.01 per cent added iodide, a salt intake of 2.0 Gm/day will meet the daily need.

The most reliable natural sources of iodine are seafoods The iodine content of vegetables depends largely upon the iodine content of the soil on which they are grown.

Copper. Copper is a necessary nutrient for man, being particularly concerned with erythropoiesis. Well-documented cases of copper deficiency in the adult are not found in the literature, but in some instances a deficiency of this element has been implicated in hypochromic anemia of infancy and early childhood.

Cartwright (1950) found that adults remain in positive copper balance if their intake stays above 2 mg/day He concludes that, "An American diet of even mediocre quality easily supplies the daily requirement." Lindow et al (1929) list the following foods in descending order of copper content· nuts, dried legumes, cereals, dried fruits, poultry, fish, animal tissues, green legumes, roots, leafy vegetables, fresh fruits, and nonleafy vegetables. Milk is a particularly poor source of copper, which may well explain the occasional response to copper therapy of the infant with a hypochromic anemia.

Other Inorganic Elements. Cobalt, zinc, magnesium, molybdenum, and manganese are commonly found in trace amounts in both animal and plant material. These elements are apparently necessary activators for certain enzyme systems, but little is known about desirable levels of intake Since these elements are widely dispersed in nature, it can be assumed that adequate amounts are present in a diet that is adequate in other respects.

Water. Man's intake of water is derived from ingested fluids, the water contained in ingested foods, and water produced in metabolic reactions A suitable daily intake from all sources usually varies between 2 to 3 liters, but under conditions of extreme heat or sweating, the intake may reach 5 to 13 liters daily. The National Research Council (1958) recommends a standard of 1 ml for each calorie of food. In general, the sensations of thirst serve as an adequate guide to intake, except for infants and sick persons

FOOD GROUPS

For the planning of practical dietaries that will ensure adequate intakes of essential nutrients, the common foodstuffs available in the United States and Canada have been formed into seven basic groups Each group contains items of similar nutrient characteristics. In order to plan a well-balanced diet, it is merely necessary to specify the number of servings from each group that is to be taken daily. Table 2-14 defines these groups and enumerates the recommended number of servings that should be taken daily in order to ensure an adequate intake of essential nutrients (McLester and Darby, 1952).

Recently, the U S. Department of Agriculture combined the first three of these groups and eliminated the last, thereby reducing the number of basic food groups to four. However, the older system is somewhat more specific and is, therefore, detailed here.

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Increased capillary permeability

W. G. SPECTOR

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EXPERIMENTAL DEMONSTRATION OF INCREASED CAPILLARY PERMEABILITY

To study the phenomenon experimentally, it is necessary to follow the time course of increased capillary permeability to protein and

[1] See also Chap 18 *Editor.*

also to assess it quantitatively. Many methods have been devised to these ends.

One of the most used techniques is to inject the test animal intravenously with an azo dye, e.g., trypan or pontamine blue, which binds firmly to the plasma albumin in vivo. Thus, when plasma protein leaks out of capillaries whose permeability is increased, the surrounding tissue becomes stained blue. Usually the skin is used for this purpose, and the size and intensity of the area of dye staining serve as a measure of the degree of increased permeability.

Another method is to measure the amount of edema itself. Thus, the increased capillary permeability that follows thermal injury of the skin may be measured by excising the burnt area and determining its content of water *gravimetrically* in grams per square centimeter. The volume of inflammatory exudate may also be used for this purpose, e.g., in pleurisy induced by intrapleural injection of turpentine. Another method is to induce increased capillary permeability in the paw of the rat and measure the resultant edema plethysmographically, or by visual estimation, or gravimetrically

Direct observation of the passage of unlabeled protein through capillary walls is not possible. The movement of dye-labeled protein has, however, been observed microscopically in transparent structures, such as the rat mesentery and frog web The accumulation in an inflammatory exudate of circulating protein labeled with radioactive iodine has also been used in making a quantitative estimate of increased capillary permeability

Another quantitative technique is the measurement of the amount of protein and water filtration from capillaries in a limb the base of which has been compressed, thus inducing venous compression A fuller account of these methods can be found elsewhere (Spector, 1958)

MECHANISM OF INCREASED CAPILLARY PERMEABILITY

Broadly speaking, there are only two ways in which protein may pass from the blood through the capillary wall through the cytoplasm of the endothelium or between the endothelial cells Any hypothesis must explain two facts concerning the increased capillary permeability after injury—the reversibility of the change, and the tendency to "molecular sieving," i.e., preferential passage of the smaller protein molecules, notably albumin

The hypothesis that *increased capillary permeability is due to microscopic gaps between the endothelial cells* is the classical view, and until very recently had the weight of evidence in its favor. Thus, the speed with which proteins leave inflamed capillaries appeared to make transcytoplasmic transport unlikely, since it seemed (and still seems) difficult for a cell to survive such a disturbance within its substance. It must be realized that even water crosses the capillary wall at a rate some hundred times faster than that at which it enters or leaves body cells. This fact suggested that water itself passes *between* the cells of the endothelium rather than passing through them.

It has been noted repeatedly that the only apparent factor governing the selective passage of proteins or other colloids through the capillary wall is molecular size (molecular sieving). This observation, too, suggested that proteins leave the capillary by some purely physical process, since cytoplasmic transport might be expected to be governed by more specific factors Passage dependent upon molecular size indicated movement of molecules through some "nonliving" constituents of the vessel wall, such as *intercellular substance*.

The theory that increased capillary permeability to protein is due to the opening up of intercellular gaps in the vessel wall owes much to Pappenheimer (1953). In an analysis of the problem, Pappenheimer suggested that proteins (and other nonlipid-soluble macromolecules) traverse the capillary wall by way of water-filled channels or *pores* His calculations led him to believe that these pores occupied only about 0.2 per cent of the total area of the wall and that the diameter of the channels was probably uniform for a given set of capillaries The effective pore radius appeared to be of the order of 44 A, although probably varying from one tissue to another

It was also suggested that transcapillary passage of protein may be governed by *restricted diffusion* In other words, the diameter of the channel may be larger than that of the largest protein molecule but certain forces may hinder its passage. One such force might be *viscous drag* between the molecule and the wall of the channel Such drag is seen between many types of sedimenting particles and the walls of their container. Another force restricting diffusion might be *steric hindrance*, i.e., inability of the protein molecule to enter

the channel *unless it* does so without first impinging on the margins of the pore.

This *analysis may* be used to explain increased capillary permeability in a variety of ways. First of all, the formation of protein-rich exudate without changes in the capillary wall would be possible if one merely postulates a great reduction in the filtration rate of water, due, for example, to lowered intracapillary pressure, relative to an unchanged rate of diffusion of protein, the two processes being independent Whether so severe a reduction of water filtration ever occurs in practice is uncertain In any event, observation indicates that in the vast majority of instances, the formation of protein-rich exudate is associated with an absolute increase in transcapillary passage of protein, rather than with a mere reduction in water filtration. Moreover, it has been suggested that permeability to protein within certain limits varies directly with intracapillary hydrostatic pressure, suggesting that protein loss, too, may be partly a filtration process

To equate Pappenheimer's analysis with the classical view of increased capillary permeability, it is necessary to postulate enlargement of existing pores, the formation *of many new* channels, dissolution of the *entire system of* water-filled channels, or loss of the forces that restrict diffusion, such loss resulting, for example, from alterations *in charge at the* pores None of these possibilities is *inherently* unlikely.

The proponents of the view that increased capillary permeability is due to *the appearance* of gaps in the vessel wall were *able to* produce a certain amount of direct *evidence* (Chambers and Zweifach, 1947) Thus, microscopic observation of living capillaries after *injury* revealed masses of material *suggestive of intercellular* cement in the process of being discharged into the lumen In addition, *evidence* of softening of intercellular *substance* was found *in the* vessel wall Study of endothelial *surfaces* also *has* revealed changes in the staining *reactions of the intercellular* "cement" (McGovern, 1955). It is possible that this intercellular substance is composed partly of *polysaccharides* If so, the observation that vascular endothelium appears to synthesize *mucopolysaccharides* (Curran, 1957) could provide a *clue* to the mechanism whereby gaps are formed in the capillary wall

These observations are concerned with the view that increased capillary permeability is due to dissolution of intercellular substance. There are, however, other theories *as to the* accelerated passage of protein through intercellular pores These theories are, in general, based on the concept that the hypothetical intercellular spaces allow rapid passage of proteins but that limiting structures which normally restrict this protein loss are removed following injury Thus, it has been suggested that an *endocapillary layer of plasma protein,* firmly adsorbed to the inner endothelial surface, serves this function (Danielli, 1940). The existence of this layer is hypothetical, but it is obvious that if it serves the function ascribed to it, its digestion or replacement (*e.g.,* by surface-active peptides) could lead to increased capillary permeability. *Fibrin* has been suggested as a *constituent of the endocapillary* layer, but there is little *direct evidence* to support this. The main advantage of the endocapillary-layer theory is that it could *explain the* ability of many peptides and of certain *proteolytic* enzymes to alter the permeability properties of the capillary wall

Another structure that may possibly limit *the* rate of protein leakage between vascular endothelium is the *basement membrane* that invests the outer surface of the capillary. In contradistinction to the endocapillary layer, the basement membrane is known to exist and is *clearly* seen in electron micrographs Its chemical composition, its properties in relation to the passage of protein molecules, and the changes within it during increased capillary permeability are all, however, as yet a matter of guesswork It is nevertheless clear that this membrane might well act as a barrier to the *escape* of protein and that its ultrastructure, *possibly a lattice* of fibers, could be suited to function as a molecular sieve *Indeed, it is* possible that it is the basement membrane *which is the site* of the system of channels postulated *by* Pappenheimer and described above Molecular *sieving* can of course result from the diffusion of molecules of varying *size through* pores of uniform radius (*restricted diffusion*), or through pores of variable radius It can also result from differences in net electrical charge on the molecules, provided *that* the proteins are passing through a

structure with some of the properties of an ion-exchange resin. The selective passage of plasma proteins through certain types of column, such as cellulose with substituted carboxyl or amino groups, provides a model of molecular sieving of this type. Moreover, it is quite possible for net charge (and therefore likelihood of retention or free passage of the molecule) to depend, under certain circumstances, largely on molecular size.

Theories based on alterations in the hypothetical endocapillary layer and in the basement membrane imply no change in the endothelium itself. However, histologic study of inflamed capillaries in a state of increased permeability usually indicates *swelling of these cells*, which tend to lose their elongated form and assume a more globular shape. Moreover, direct study of lining capillaries after local application of hypertonic sugars seemed to reveal contraction of endothelium and the resultant appearance of gaps in the capillary wall through which red corpuscles were observed to pass (Chambers and Zweifach, 1947).

The subject of the *contractility of endothelium* cannot be discussed in detail here. However, normal consequences of such contraction might be expected to be capillary vasoconstriction and reduced permeability. It seems, therefore, that the endothelial contraction caused by hypertonic sugar solutions is probably of a different nature It is easy to imagine that as capillary endothelia contract or shrink away from each other, gaps might form between the cells in the vessel wall. Such a process could be akin to the active shortening of fibers that occurs when muscle contracts in response to appropriate stimulation. Suitable attached muscles assume a more globular form on contraction, and so might capillary endothelium. The rounded shape of inflamed vascular endothelium could equally well, however, result from swelling due, for example, to influx of water, sodium, and chloride, as occurs in injured cells generally

It seems likely that some reversible mechanism must exist for the separation of endothelial cells in the capillary wall This is so because, after injury, large numbers of leucocytes pass through the capillary wall into the tissues and can be clearly seen actively making their way between the endothelial cells. Obviously, leucocytes must leave the vessels in this way, but plasma protein molecules, the other major constituent of inflammatory exudate, can theoretically traverse the cytoplasm of living endothelium Careful electron-microscopic study of capillaries before and during increased permeability to protein (not to leucocytes), however, fails completely to reveal any evidence of intercellular gaps in the vessel wall.[2] Previous studies of normal capillaries had led to a similar conclusion (Karrer, 1956). The electron micrographs of capillaries rendered permeable to protein by application of *histamine* showed, on the other hand, a great increase in the number and size of the small, clear vacuoles that exist normally in the cytoplasm of capillary endothelium In places, these vacuoles were seen to coalesce and thus form intracytoplasmic channels, sometimes stretching across the cell from the luminal to the external margin (Alksne, 1959). Colloidal suspensions of heavy metals in the circulation could be seen passing through the capillary walls by way of the endothelial cytoplasm. A high proportion of particles in course of transport appeared to lie within the intracellular vacuoles.

Several speculative inferences might be drawn from these studies. The repeated failure of skilled observers to detect intercellular pores or gaps undoubtedly strikes a severe and possibly mortal blow at the classical pore or gap theory of increased capillary permeability. Against all probability, the results of electron microscopy indicate that plasma protein leaves these vessels by the transcytoplasmic route The great increase in intracytoplasmic vacuoles may indicate that these bodies are part of a transport system for plasma proteins. If so, it must be assumed that injury in some ways greatly increases the activity of this system The effect might be achieved by direct stimulation of the transport mechanism or by indirect activation, which is perhaps more likely. Such an indirect effect might result from the diversion of available energy to the transport system because of the blockage by injury of other, less hardy energy-requiring reactions.

Other electron micrographs of capillaries in a state of increased permeability suggest not so much increased vacuolation as *partial dis-*

[2] For a more recent and contrary view see Palade

solution of the endothelial cytoplasm Such pictures raise the possibility that, rather than stimulation of a physiologic mechanism, there is breakdown of this transport system and its replacement by a less-organized movement In any event, electron microscopy indicates that the *water-filled channels*, postulated as the pathway by which proteins leave capillaries, may perhaps exist within the endothelial cytoplasm A system of this nature may seem bizarre in mammalian physiology If, however, vascular endothelial cells are considered as representatives of the primitive, phagocytic, ultrapotent cells that line channels in the simplest organisms, and as descendants of the protozoans themselves, these properties, while still remarkable, seem less inherently unlikely. Once it is accepted that there may be a pathway for the rapid transcytoplasmic movement of plasma protein through vessel walls, it seems of less consequence to label this process categorically as either transport (as in renal tubule cells), on the one hand, or diffusion through water-filled *channels*, on the other

A new aspect of capillary permeability has been revealed by recent work on the antihistamine compounds It has been known for a long time that in high concentrations, these drugs will diminish increased capillary permeability resulting from stimuli other than the application of histamine, so that they *have a general antipermeability action on capillaries*

It was then found that antihistamine drugs had the remarkable properties of *preventing necrosis of the liver* due to hepatic poisons, such as thioacetamide and carbon tetrachloride, to dietary deficiency, and to murine hepatitis virus (Rees, Spector, and Sinha, 1961, McLean, 1960; Judah et al, 1960) It was also discovered that the antihistaminics prevented the *loss of potassium and uptake of water and sodium*, characteristic of liver cells from rats in a state of dietary deficiency (McLean, 1960). *Finally*, the antihistamine drugs were found to prevent similar electrolytic changes in hypoxic liver cells and also to prevent these *phenomena* in injured isolated mitochondria (Judah, 1960) The substances also inhibit the shrinkage of isolated mitochondria when the particles are restored to a more normal environment

It follows from these experiments that the antihistamine drugs have a general depressant effect on the permeability of cells and mitochondria to electrolytes (the term *permeability* is here used in its loosest sense). In parallel with their other effects, the compounds depress the incorporation and release of phosphate into and out of intracellular phosphoprotein It has been suggested, therefore, that phosphoprotein plays a role in the maintenance of electrolyte gradients by the cell, breakdown of the molecule being associated with loss of cellular potassium and uptake of sodium and water, and vice versa. It has also been suggested that the antihistamine drugs affect cellular electrolyte movements by virtue of the action of the drugs on the phosphoprotein system (Judah, 1960) The precise relationship of phosphoprotein to electrolyte movement is a matter of speculation. The phosphoprotein could be part of a specific ion-binding matrix, or *act as a contractile* fibrillar molecule, or be a *source of* high-energy bonds feeding some type of energy-dependent transport system.

Because of the *parallel actions of* antihistamine drugs on capillaries, smooth muscle, and *cells and cell particles, it is* legitimate to consider *whether their effects* reveal a basic *underlying* mechanism Thus, it could be argued that certain unfavorable environmental *changes* (i e., "injury") lead to basic acute changes manifested as *increased permeability to* protein by capillaries, and as inability to *maintain* ionic gradients by cells and mitochondria It is known *that damaged cells* may *lose their* soluble proteins as well as their potassium, and it is possible that this *protein loss* may be analogous to *the escape* of plasma protein through *inflamed vessels*. These views are of course compatible with the electron-micrographic evidence suggestive of increased *protein transport* in the endothelium of capillaries in a *state of increased* permeability. It may also be significant that the local removal of *ionized calcium by* addition of chelating agents. such as Versene, to the environment, leads to *increased* permeability to protein in the case of *capillaries* and to loss of potassium and uptake of *water and* sodium by liver cells and *mitochondria* *Most* directly of all, one may make a comparison *between* the cell membrane of the *capillary* endothelium in a

state of increased permeability to plasma protein and that of an epithelial cell or other type of cell that is losing potassium. In other words, the essential change in increased capillary permeability may lie in the endothelial membrane, not in the intracellular transport system. In current studies on the structure of cell membranes, the concept of pores of molecular dimensions and of labile diameter is still accepted (Conway, 1960). Such pores are consistent with the process of restricted diffusion as postulated by Pappenheimer for capillaries and plasma protein It seems therefore, that *in order to integrate Pappenheimer's analysis with the results of electron microscopy, it is necessary only to accept the fact that plasma protein leaves capillaries via the endothelial cytoplasm.*

INCREASED CAPILLARY PERMEABILITY IN INFLAMMATION

Thus far, increased capillary permeability has been considered as a biologic phenomenon initiated by injury. It is in fact a cardinal feature of one of the most basic defensive reactions of animal life, viz., inflammation. *Inflammation is the local reaction to injury of living tissues, in particular the small blood vessels, and results in the exudation into the tissues of water, salts, plasma proteins, and leucocytes* In invertebrates, such as the earthworm or the leech, because there is no circulation in the mammalian sense, inflammation is confined to proliferation and increased activity of phagocytes

In mammals, inflammation is a cyclical phenomenon which begins as transient vasoconstriction, followed by prolonged dilatation of arterioles, venules, and capillaries At this stage, *increased capillary permeability to protein* develops, there is endothelial swelling, and polymorphonuclear leucocytes adhere to vessel walls, having left the center of the blood stream Within a matter of hours after injury, emigration of polymorphs through the walls of capillaries and venules is apparent on a large scale, infiltration of the tissues reaches its height at about 24 hr. If the injury is not repeated or prolonged, the inflammatory reaction now enters the subsiding phase of its cycle. Capillary permeability and blood flow return to normal, the latter having previously been first accelerated and then slowed. The polymorphs in the tissues may be replaced by macrophages and later by fibroblasts and lymphocytes. If tissue has been destroyed, healing will occur by ingrowth of new blood vessels, lymphatic vessels, and nerves, and fibroblasts will lay down collagen to form a scar.

There are many forms of inflammation far more complex than the simple reaction described above. Such complex reactions include those occurring in tuberculosis, typhoid, leprosy, and many other specialized infections Even in these cases, there is usually a brief period at the initiation of the reaction during which classical acute inflammatory changes may be recognized. The specific features of the above diseases, and *in particular the characteristic nature of the cellular exudation associated with them, may represent modifications of that phase of classical inflammation in which invasion of macrophages dominates the scene and which teleologically indicates a defensive reaction to particulate matter.* In other words, the chemical and biologic peculiarities of some microorganisms may affect the cellular response to their presence.

It is possible to put the above diseases (*infective granulomas*) into the cyclical pattern of inflammation. In other cases, however, it is less easy. Thus, in *Hashimoto's disease, or lymphocytic thyroiditis,* the thyroid gland is infiltrated with lymphocytes and plasma cells, an exudate that is usually regarded as indicating chronic inflammation, or rather a prolongation of the mononuclear phase of the inflammatory reaction However, in many cases there is no evidence that this picture is preceded by acute inflammation with polymorphic exudation. It seems possible, therefore, that a modified type of reaction may exist which consists from the beginning of the accumulation of lymphocytes and plasma cells *In the light of current views of* Hashimoto's disease, this response could be regarded not so much as inflammation as the accumulation of antibody-producing cells at a site of antigen Indeed, the presence of plasma cells, if not of lymphocytes, is probably an indication of antigen stimulation in all forms of inflammatory reaction.

In spite of all this, the experimentally proved reaction of living tissues to antigen-antibody combination is a classical acute inflammatory

response as seen in *Arthus' reaction*, or *passive cutaneous anaphylaxis*, or in the vascular lesions of *serum sickness*. Increased capillary permeability and polymorph emigration are the chief manifestations of these lesions.

The example of inflammation of most interest to cardiologists is *rheumatic fever*, and this disease bears many similarities to experimental disease caused by antigen-antibody reaction. The acute, or exudative, phase of rheumatic fever is characterized by classical increased capillary permeability to protein. The clinical manifestations of this phase are the typical fibrinous pericarditis, local areas of exudation in myocardium and endocardium, acute arthritis with effusion of protein-rich fluid, and exudative skin lesions. When the rheumatic inflammation enters the proliferative, or "macrophage," phase, the characteristic lesion is the *Aschoff body*, which is essentially a collection of antibody cells (plasma cells), lymphocytes, and modified macrophages. "Fibrinoid" probably represents polymerized fibrinogen, the protein having escaped from permeable capillaries. If the injurious stimulus is overcome or withdrawn, the cell collections are replaced by fibroblasts, which convert the lesion to a fibrous scar, in which a few lymphocytes may survive. It is easy to see that the chain of events leading to the permanently scarred rheumatic heart begins as increased capillary permeability. All successful therapy has had as its aim the suppression of this phenomenon, its importance in rheumatic fever would alone justify the inclusion of this article in an encyclopedia of cardiology.

All this discussion leads up to one question, fundamental both to understanding and to therapy: what is the link between all the multifarious types of injury and the vascular events of inflammation? How does injury cause increased capillary permeability?

Any answer must explain certain basic facts, the ability of many different types of injury to cause identical tissue changes, the initiation of inflammation by transient stimuli such as heat, in which nothing material is added to the tissues, the cyclical nature of the inflammatory reaction, in which one phase leads in orderly fashion to the next, and, very important, the reversible nature of the vascular changes.

These facts indicate that the true cause of inflammation lies in the tissues themselves and that injury may initiate inflammation by activating an endogenous mechanism. The nature of this hypothetical endogenous mechanism has been the subject of much research; there is considerable evidence to support what is termed the "chemical mediator hypothesis," i.e., the release or activation by injury of endogenous substances in or near the vessel wall whose pharmacologic properties enable them to bring about the vascular changes of inflammation. This hypothesis is sometimes criticized on the ground that the possibility of direct action of injury on the blood vessels is seldom considered. It is obvious, however, that some common pathway must be involved. This final path could be the release of chemical substance from the vicinity of the vessels or denaturation of a protein, or activation of an enzyme or other substance in the vessel wall itself. It is clear, however, that some chemical reaction or reactions must intervene between injury and vascular reaction, the only alternative being physical or chemical destruction of the vessel, an explanation ruled out by the reversibility of the changes and by the ability of certain drugs to prevent injury from inducing inflammatory phenomena. *Indeed, inflammation is by definition the reaction of living vessels to injury.* These statements contain the essence of the so-called "mediator" hypothesis. To attempt too rigid a distinction between release of vasoactive compounds and activation of mechanisms in the vessel wall itself is premature. It is almost certain that both types of reaction are involved.

ENDOGENOUS SUBSTANCES INVOLVED IN INCREASED CAPILLARY PERMEABILITY

Histamine.[3] This substance is a diamine derived from the amino acid histidine by action of the enzyme histidine decarboxylase. Its structural formula is as follows.

```
                        NH2
                        |
HC=====C—CH2—C—H
|              |              |
N            NH            H
  \\        /
      C
      H
```

[3] See also Part 21, Chap. 8 Editor

state of increased permeability to plasma protein and that of an epithelial cell or other type of cell that is losing potassium. In other words, the essential change in increased capillary permeability may lie in the endothelial membrane, not in the intracellular transport system. In current studies on the structure of cell membranes, the concept of pores of molecular dimensions and of labile diameter is still accepted (Conway, 1960). Such pores are consistent with the process of restricted diffusion as postulated by Pappenheimer for capillaries and plasma protein. It seems therefore, that *in order to integrate Pappenheimer's analysis with the results of electron microscopy, it is necessary only to accept the fact that plasma protein leaves capillaries via the endothelial cytoplasm*

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The discrepancy between anaphylactic and other types of injury may, therefore, be due to the fact that, in anaphylaxis, histamine release and other powerful vasoactive mechanisms develop simultaneously and explosively, whereas in the other instances the two endogenous mechanisms come into play serially or more slowly.

It is clear that, apart from the direct evidence of histamine release after injury and of the effect of histamine depletion in turpentine pleurisy, much of the case for the role of histamine in inflammation is derived from the use of antihistamine drugs. It is well known that high doses of some of these compounds, notably the phenothiazines and especially promethazine hydrochloride (*Phenergan*), cause a general suppression of increased capillary permeability to agents other than *histamine*. This raises the possibility that the so-called antihistamine effect is merely a manifestation of a general antipermeability effect, the two differing only on a quantitative basis. It seems possible that this question could be resolved by *direct experiment*. In the meantime, however these drugs act, the relevant doses of mepyramine are, as far as can be ascertained, antagonistic only to histamine. This fact, coupled with the unequivocal results of histamine depletion by compound 48/80 and the results of *histamine* assays, does indicate that histamine plays a *causative* role in the development of *increased* capillary permeability after injury. *This role, however, is subsidiary in the sense that histamine seems only to initiate the changes. The maintenance of increased capillary permeability is due to the operation of various other endogenous mechanisms.*

MECHANISM OF HISTAMINE RELEASE. The source of all the histamine released by injury is not known with *certainty*. Because mast cells are rich in the substance and because these cells disintegrate after injury, it seems probable that a good deal of the liberated histamine comes from their cytoplasmic granules. Another likely source is the blood platelets, which also contain histamine and are likely to be disrupted by injury.

A variety of compounds are known which release histamine from tissues and from mast cells in particular. The most potent of these substances is compound 48/80, but many other types of molecules share this property, ranging from *detergents* to *complex polysaccharides*. Their mode of action is uncertain. Suggested mechanisms include alteration of the mast cell membrane, rupture of a peptide bond linking histamine to a protein, rupture of a polar linkage to a protein or lipoprotein, or breaking a combination of histamine with an acidic substance by means of an ion-exchange reaction.

Most of these suggestions could apply equally well to the liberation of histamine by injury or antigen-antibody reactions. There is considerable evidence, however, that, in these circumstances, histamine release is an *active metabolic process* rather than a purely physicochemical phenomenon. Uvnas (1958) suggested that situated on the mast cell membrane is an enzyme possessing amino groups, possibly a carbonic esterase akin to lecithinase, together with a *specific inhibitor of this enzyme*. He proposed that histamine release follows inactivation of the *inhibitor*, the enzyme then attacking the mast cell membrane. Subsequent work has indicated that the release of histamine from mast cells is the result of activity by proteolytic enzymes on or within *the cell, and that these* proteases belong to the category in which esterase activity is also present (Glennor and Cohen, 1960). The precise mechanism whereby injury of diverse types might activate such enzymes remains a mystery which lies at the heart of the inflammation problem.

MODE OF ACTION OF HISTAMINE ON CAPILLARY PERMEABILITY. This is unknown. High concentrations lead to weakening of the wall and diapedesis of red cells, but this is probably a separate phenomenon. The presence of *histamine leads* to increased vacuolation in capillary endothelium on *electron* micrography, and this may indicate increased protein transport through the cytoplasm (see above). It may *be that histamine* has general properties affecting the permeability of cells. Thus, it causes a slow swelling of isolated liver mitochondria, presumably *because* of uptake of water and loss of potassium (Judah, unpublished). It could be argued that a similar effect of histamine on cell permeability leads to that *characteristic* loss of protein through the capillary wall which is seen *after* injury.

Histamine is very widely distributed in the body tissues. The mast cells that adjoin blood vessels are particularly rich in the substance. Histamine dilates capillaries and, with increasing dosage, causes progressive increase in capillary permeability to protein. It also leads to dilatation of arterioles in some species, including man.

With these properties, it is easy to see why histamine was thought of as a possible mediator of vascular changes after injury. Lewis drew attention to the similarity between the "triple response" of skin vessels to minor damage and the similar response to intradermal injection of histamine. From this comparison, he evolved the well-known suggestion that *injury liberates a histamine-like substance at the site of damage*. Since that date, a great mass of evidence has been collected in support of his hypothesis, indicating that the "histamine-like substance" is in fact histamine Thus, signs have been found of histamine release in tissues damaged by *burns, chemical irritants*, and *bacterial invasion* Such experiments were based on histamine assay of the excised tissues. More reliable data have been obtained by examination of blood and tissue perfusates. These observations showed again that injury causes the liberation of histamine from its binding in the tissues. *Anaphylactic injury*, due to combination of antigen and antibody, causes the release of histamine into the blood stream in a number of species, and a similar phenomenon is demonstrable in the perfusates of sensitized organs on addition of antigen. Release of histamine has also been shown in vitro following the addition of antigen to sensitized leucocytes and platelets and to sensitized minced tissues from a number of organs and species, including human lung. The release of histamine after injury is virtually instantaneous, and the substance does not persist for long Thus, in pleural exudates produced by intrapleural injection of turpentine, histamine is demonstrable only during the first 30 min after injury The appearance of the substance in the circulation after anaphylaxis is equally transient Further details of these numerous investigations will be found elsewhere (Wolstenholme and O'Connor, 1956, Spector, 1958).

Demonstration of histamine release following injury does not prove that the substance is responsible for the vascular changes of early inflammation. Fortunately, some of the antihistamine drugs (although not all) are in certain doses, and as far as can be ascertained, virtually specifically antagonistic to histamine Thus 1 mg/kg of mepyramine maleate (*Anthisan, Neo-Antigan*), given systemically, suppresses increased capillary permeability due to injection of histamine but not to other compounds with a similar action on vessels. Similar doses of mepyramine delay the onset of increased capillary permeability caused by intrapleural turpentine or by thermal injury of the skin from 30 to 90 min (Spector and Willoughby, 1959a, b). After this time, increased capillary permeability develops unhindered, even if further doses of mepyramine are given. These results, obtainable in both rats and guinea pigs (Wilhelm, 1959), indicate that the initiation of increased capillary permeability, at least in some types of injury, is due to local release of histamine and that other mechanisms then become important in the maintenance of altered permeability.

This interpretation is confirmed by the results obtained with *compound 48/80* This substance is a complex organic base; repeated injections of it lead to almost total depletion of the bodily stores of histamine Rats so depleted, following intrapleural injection of turpentine, display a delay in the onset of increased capillary permeability similar to that caused by premedication with specifically antihistamine drugs (Spector and Willoughby, 1959a).

Many clinical manifestations of increased capillary permeability, e g., *hay fever* or *urticaria* due to antigen-antibody reaction, are diminished by specific antihistamine measures. Indeed, there is no serious opposition to the view that histamine plays a role in some allergic vascular reactions. However, in acute inflammatory reactions induced in the rat by active or passive cutaneous anaphylaxis, prior administration of doses of mepyramine specifically antagonistic to histamine, fails to modify the course of events (Brocklehurst et al, 1960). In these experiments, however, maximal increased capillary permeability develops within 25 min. In turpentine-induced pleurisy, the height of the changes is not reached for at least several hours and, in cutaneous thermal injury, not for 2 to 3 hr.

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5-Hydroxytryptamine (Serotonin, 5-H.T.).[4] In most species, this substance, which is a monoamine derived from the amino acid tryptophan, is a vasoconstrictor. In the rat, however, low concentrations cause increased capillary permeability. In addition, specific antagonists of 5-H.T. diminish the increased capillary permeability caused by injection of certain substances that liberate 5-H.T. in the rat. Moreover, 5-H.T. is demonstrable in turpentine-induced inflammatory exudates in the first 30 min after injury. For these reasons, it seemed possible that 5-H.T. might play a parallel role to histamine in causing increased capillary permeability after injury in the rat, if not in other species. However, the failure of 5-H.T. antagonists to lessen or delay increased capillary permeability after physical and chemical injury did not confirm this hypothesis. A fuller discussion of these matters will be found elsewhere (Spector, 1958). On the other hand, a 5-H.T. antagonist (bromo-lysergic acid diethylamide tartrate, BOL 148) does diminish the increased capillary permeability due to passive cutaneous anaphylaxis in the rat. The significance of this observation remains uncertain.

Peptides and Capillary Permeability. Peptides are molecules consisting of amino acids joined together by peptide linkages to form units too small to be considered proteins. Generally speaking, they may be differentiated from proteins by the ability to diffuse through semipermeable membranes such as celloidin, i.e., to be dialyzable. Peptides possess an enormous diversity of biologic properties, and it has been known for a long time that certain complex mixtures containing peptides, such as bacteriologic "peptone," had striking effects on small blood vessels. However, it was shown that albumin, following partial digestion by trypsin, acquired the ability to increase capillary permeability (Menkin, 1956). Menkin achieved a partial separation of the active principle, which he called "leucotaxine" by virtue of its parallel effect in inducing leucocyte emigration. He believed that "leucotaxine" had been obtained in a high state of purity in a crystalline form, but subsequent work showed that this was not so.

Menkin's observations were soon confirmed by other investigators, and it rapidly became apparent that a large number of combinations of proteolytic enzymes and protein substrates would yield products able to increase capillary permeability (Spector, 1958). Further work revealed that in a typical active peptide mixture, the action on capillary permeability was related to the number of amino acids in the peptide molecule. Below five amino acid residues, no vasoactivity was present, and the average chain length of the permeability-increasing peptides was about eight amino acids (Spector, 1951). The validity of these findings was subsequently confirmed when new techniques made it possible to purify an example of a peptide that affects capillary permeability (Elliot et al., 1960) and the peptide in question (*bradykinin*) was found to possess nine amino acids in its molecule.

The attention of investigators was then turned away from peptide mixtures to specific peptides formed within the body. These peptides are termed *kinins;* they stimulate plain muscle as well as affecting small blood vessels. Such substances include *substance P, bradykinin, kallidin, substance U,* and others. Of these, bradykinin and kallidin seem likely to be of most importance. Both these peptides are formed from the α_2-globulin of serum but by the action of different enzymes. So far, it has proved difficult to distinguish between the two peptides by chemical or pharmacologic means. These compounds increase capillary permeability in all species, some animals, like the guinea pig, being more sensitive than others. Much progress has been made in isolating and purifying these substances, complete success has been achieved with bradykinin.

The earlier work was based on the hypothesis that injury might lead to widespread proteolysis and thus give rise to peptide formation. Subsequent investigation suggests that, on the other hand, injury gives rise to the formation of specific peptides by activation of a specific enzyme system. Thus when plasma is brought into contact with a charged foreign surface, such as glass, there is rapid formation of peptides indistinguishable from bradykinin or kallidin. A similar result is obtained when plasma is diluted with saline solution. In all these instances, the peptides enjoy only a very brief existence, being rapidly destroyed by plasma peptidase. In vivo, transient forma-

[4] See also Part 21, Chap. 7. *Editor.*

tion of peptides has been demonstrated in the circulation of dogs subjected to anaphylactic shock.

In the past, certain fractions of 24- or 48-hr-old inflammatory exudate have been thought to increase capillary permeability by virtue of their peptide content. More sophisticated and recent experiments have indicated that in early inflammatory exudates, when the vascular reaction is at its height, little or no permeability activity referable to peptides can be demonstrated. This result contrasts with the powerful vascular effects of these compounds but is easily explained by the rapid destruction of such peptides in the body.

It is impossible to consider the role of vasoactive peptides in inflammation without parallel discussion of a group of proteins, viz., the proteolytic enzymes and protein substrates whose interaction leads to peptide formation. With regard to substrate, the chief source in vitro of the peptides under discussion is the α_2-globulin, and it seems likely that this protein, in plasma, lymph, and tissue fluid, would be the major source in inflammation in vivo.

With regard to *enzymes,* there are two main possibilities. The first is the main *plasmin* or *fibrinolysin system* of the plasma. This enzyme, however, does not appear to increase capillary permeability or to cause the formation of vasoactive peptides. The second and more important enzyme is *kallikrein*. This protein, which has a molecular weight of 48,000, has a widespread distribution in tissue fluids, including serum. It is extremely active in forming the permeability-increasing peptide kallidin on incubation with α_2-globulin or whole serum. Kallikrein will presumably catalyze the formation of this enzyme in vivo, since injection of the enzyme into the skin is followed by a local increase in capillary permeability. Kallikrein exists in serum in an inactive form. It is activated, however, by the same procedures—e.g., dilution, contact with glass—that lead to the formation of peptides in plasma. It seems likely, therefore, that the appearance of these peptides is due to activation of an enzyme indistinguishable from kallikrein (Bhoola et al., 1960). The peptides so formed are themselves indistinguishable from kallidin. The action of kallikrein may be true proteolysis, or it may be that of an esterase, which is perhaps more likely. Its characteristics suggest that it belongs to the group of enzymes, such as trypsin and chymotrypsin, that possesses both types of activity.

There is considerable evidence that injury leads to the activation of proteolytic enzymes in vivo. Thus, the appearance of protease activity in the blood of the dog during anaphylaxis is well documented. In other systems, there is some dispute as to the appearance of proteolytic activity. Much of the confusion may well be explained by the fact that activated proteases, like the peptides they give rise to, may exist only transiently before themselves being destroyed. Other confusion resulted from the erroneous assumption that the protease activated by injury belonged to the plasma fibrinolysin system. In fact, kallikrein has no fibrinolytic activity.

Another protein of particular importance to capillary permeability was described by Miles et al. (1955). It exists in the globulins of serum from all species tested, either in the α_2 or β fraction. This globulin exists in an inactive form and is activated by dilution, by contact with glass, by the addition of ether, or by incubation with disrupted cells. Also present in a different fraction of the plasma proteins is a specific inhibitor of the permeability-increasing globulin. It is obvious that many similarities exist between this globulin and serum kallikrein. In addition, soya bean-trypsin inhibitor prevents the action of both compounds. There is no direct evidence that the permeability globulin is a protease or esterase, but a high degree of substrate specificity must be expected in view of the properties of kallikrein, e.g., its failure to digest fibrin. There is the possibility that the globulin might be a specific substrate for the formation of a kallidin-like peptide by the action of tissue proteases. It seems on the whole more likely, however, that it is part of an enzyme system akin or identical to kallikrein.

Although it has proved difficult to demonstrate the presence of kinins in inflamed tissues at the height of the vascular changes, more success has been achieved with the permeability-increasing globulins. Following intrapleural injection of turpentine in the rat, increased permeability develops in the pleural capillaries and reaches its peak in 3 to 6 hr. Over the same period, the pleural exudate is found to contain *permeability*-*increasing glob-*

ulins in a fully activated state. As the capillary permeability declines with the resolution of the inflammatory process, so the permeability-increasing globulin in the pleural exudate reverts to the fully inactive state, becoming even less active than that of fresh serum. Activation following injury is partly due to the reduction in the amount of specific inhibitor available and partly to changes in the permeability-increasing globulin itself. These results suggest a causative role of the globulin system in increased capillary permeability after chemical injury (Spector, 1958).

Studies with specific inhibitors have proved less rewarding in the plasma protein-kinin system than for histamine. Soya bean–trypsin inhibitor antagonizes the system in vitro, but it has not yet proved possible to obtain this effect in vivo On the other hand, salicylate, DFP (di-isopropylfluorophosphate), and quinine inhibit activation of the globulin system in vitro, and also suppress the development of increased capillary permeability after a variety of injuries in the rat, including thermal injury of the skin, turpentine-induced pleurisy, radiation injury of the bowel (Willoughby, 1960), and proteinuria from various causes (Carone and Spector, 1960) The mode of action of salicylate in turpentine pleurisy is such as to suggest that the drug is inhibiting a system that comes into operation only after histamine has exerted its effect, but that the system is not dependent upon the effective release of histamine for its successful operation This effect of salicylate in suppressing the increased capillary permeability that develops an hour or more after injury is consistent with the hypothesis that the globulin-kinin system normally maintains increased capillary permeability after histamine has initiated this vascular change (Spector and Willoughby, 1959a).

Salicylate, quinine, and DFP all have in addition another action, that of causing a general suppression of increased capillary permeability due to such agents as histamine, 5-H T, kinins, globulins, and proteases (Spector and Willoughby, 1960a) This property complicates the interpretation of inhibition experiments. It also, however, possibly yields one of the few clues as to the final mechanism in the vessel wall responsible for increased permeability. This is so because all the inhibitors are antagonists of the carbonic esterase group of enzymes or of those proteases that share esterase activity. *It may be, therefore, that increased capillary permeability depends ultimately upon activation of an esterase-protease system in or on the vessel wall* It is by no means far-fetched to postulate that a similar enzyme system, sensitive to the same inhibitors, might control the activation of the *globulin-kinin mechanism.*

Up to this point, increased capillary permeability after injury has been considered as a result of changes in the vessel wall or of the release of substances that increase vascular permeability directly. Subsequent evidence, however, has suggested that these mechanisms may be augmented by the *local inactivation following injury of vasoconstrictor amines,* which, if allowed to exert their effect, would suppress capillary permeability and prevent the development of the vascular changes of inflammation. The evidence suggests that the mechanism of this inactivation is enzymic and due to monoamine oxidase, that the vasoconstrictor amine resembles or is identical with arterenol, that injury causes both the release and the subsequent inactivation of the amine; that both events occur locally at the site of injury, that the source of the amine is neither the adrenal glands nor adrenergic nerve endings but possibly vessel walls or platelets The experimental evidence for these conclusions is based on the suppression of increased capillary permeability after injury by *inhibitors of* monoamine oxidase, by the reversal of this inhibition by compounds that inactivate epinephrine, e.g , *Dibenamine;* by the simulation of the inhibition by arterenol itself (and not by other amines), by potentiation of the inhibition by *bretylium tosylate,* which potentiates free arterenol and antagonizes adrenergic nerves, and on failure of total adrenalectomy to prevent the inhibitory effect of monoamine oxidase inhibitors (Spector and Willoughby, 1960b)

A picture has now been presented of the possible mechanism of increased capillary permeability in acute inflammation, based on the hypothesis of local release, activation, or inactivation of endogenous substances with the appropriate pharmacologic properties. The evidence is based on study of the properties of these compounds, a demonstration of their

presence at the relevant place and time, and of their subsequent disappearance when the vascular reaction subsides; on activation of the substances in vitro by techniques that may simulate events after injury, e.g., contact with damaged cells; and on suppression of increased capillary permeability by measures antagonistic to one or more of the endogenous compounds.

It would certainly be unwise to accept this picture as final, and it is possible that some of the basic premises are incorrect. Thus antihistamine drugs, even at their most specific, may inhibit increased capillary permeability after injury through a mechanism not directly involving histamine. Nevertheless, it is possible to present a fairly coherent reconstruction based on substantial evidence. The initial event appears to be *local release of histamine* occurring immediately after injury. The effect of histamine release seems to be no longer apparent after a period of up to 2 hr. The histamine probably comes from mast cells and possibly from platelets, and release from mast cells may be due to *activation of a protease or esterase on the cell wall*, which attacks the cell membrane. Histamine release is then succeeded by another mechanism, which seems most likely to be *activation of a protease-esterase system in plasma*, distinct from plasma fibrinolysin. Kallikrein and permeability-increasing globulin may represent different facets of this enzyme system. Activity of these enzymes leads to the formation from plasma proteins of *peptides (kinins), such as kallidin and bradykinin, which increase capillary permeability*. Simultaneously, there may be local release of an arterenol-like substance, which would suppress the vascular changes, were it not immediately inactivated in the tissues, apparently by monoamine oxidase.

With regard to the mode of action of these compounds on capillaries, two clues exist. High doses of certain antihistamines and a variety of antiesterases inhibit the action of all substances that increase capillary permeability. The effect of high levels of antihistamines suggests that a general permeability change in the vascular endothelium may be produced, possibly involving phosphoprotein turnover, and the action of the antiesterases suggests activation of an enzyme of the esterase-protease group in the vessel wall.

It is obvious that significant differences must exist in the operation of these chemical "mediators" after different types of injury, even in one species. Thus, in the rat, turpentine injury of the pleura gives evidence of definite separation of histamine and posthistamine phases (Spector and Willoughby, 1959a). In thermal injury, this separation is still demonstrable, although rather less clear-cut (Spector and Willoughby, 1959b). In acute injury of the skin due to antigen-antibody combination, events are telescoped into a period of 20 min, and a histamine phase cannot be separated, so that histamine release and activation of other mechanisms may be presumed to occur simultaneously, the latter proving the dominant system (Brocklehurst et al., 1960). In irradiation injury of the bowel, histamine and posthistamine phases seem to occur in spite of the intervention of a latent period of at least 24 hr between injury and apparent histamine release (Willoughby, 1960). On the other hand, in damage to the renal glomerulus due to antigen-antibody combination, no separate histamine-induced stage of proteinuria could be demonstrated, although possibly for technical reasons (Carone and Spector, 1960).

CAPILLARY PERMEABILITY AND LEUCOCYTE EMIGRATION

So far, there have been two possible explanations of the emigration of polymorph leucocytes from blood vessels in acute inflammation: either the cells leave in consequence of the same changes that result in increased permeability to protein, or their movement is in response to chemotactic stimuli in the injured tissues.

It is a fact that all substances which on injection into the skin increase capillary permeability to plasma protein will in high or very high concentration cause some leucocyte migration from vessels. Some substances are more powerful than others, histamine being weaker in this respect than certain peptide preparations. Nevertheless, compared with their action on permeability to protein, all these compounds have a relatively feeble effect on leucocytes. Their powers seem inadequate to explain the considerable polymorph infiltration seen in many types of sterile inflammation, e.g., thermal, chemical, or anaphylactic injury.

Similarly, the chemotactic effect on leucocytes of many types of bacteria, living and dead, is well known. Certain polysaccharides from animal, vegetable, and bacterial sources are also chemotactic to polymorphs. On the other hand, extracts of minced tissues, when tested by adequate techniques, do not appear to possess this in vitro property. Previous results indicating the contrary can probably be attributed to nonchemotactic forces such as convection currents (Harris, 1954).

In spite of their chemotactic powers in in vitro systems, there is no certainty that such substances will cause leucocyte emigration in vivo. Thus, the injection into the skin of *chemotactic starch granules does not cause* polymorphs to leave the vessels (Spector and Storey, 1958). Indeed, there seems no reason why a chemotactic influence should induce white cells to leave a blood vessel whose wall is in a completely normal state However, where the properties of the capillary are modified by injury, perhaps due to the action of endogenous chemical substances, it seems likely that a source of chemotaxis in the tissues could cause a massive accumulation of leucocytes outside the vessels. This set of circumstances seems most likely to occur in bacterial infection. A not yet explained discrepancy in the chemotaxis hypothesis is the ability of certain bacteria, such as the typhoid bacillus, to induce strong chemotaxis of polymorphs in vitro while the lesions they cause in vitro are typically characterized by absence of these cells

It seems clear that neither increased capillary permeability to protein nor chemotaxis provides by itself a fully satisfactory explanation of leucocyte emigration in acute inflammation There remains a third possibility, viz , some alteration in the vessel wall allowing easy passage of leucocytes, which is distinct from altered permeability to protein. Leucocytes must pass between endothelial cells As it seems likely that protein may leave by transcytoplasmic movement, consideration of leucocyte emigration and protein loss as separate entities is quite feasible. There is in fact a good deal of evidence in favor of such a separation. Thus, after thermal injury to skin, increased capillary permeability to protein reaches its peak at 1 hr and has almost disappeared by 3 hr. However, leucocyte emigration is often scarcely demonstrable by 2 hr, and does not reach its highest intensity until 4 or 5 hr. Similarly, an intradermal injection of histamine causes an increase in capillary permeability beginning within a few minutes and subsiding within half an hour. Sections of the injection site reveal that emigration of leucocytes does not begin until 2 hr after injection and is not at its height until 4 hr. Leucocyte emigration follows a similar time course after injection of sterile saline solution that causes no significant increase in capillary permeability to protein at all.

This delayed onset after even trivial insult *suggests the slow activation of a specific endogenous* mechanism. One possibility is the release of an active substance from the slow disintegration of leucocytes themselves, trapped on the surface of vascular endothelium rendered swollen and "stocky" by injury. In fact intradermal injection of leucocyte extracts causes considerable leucocyte emigration, which is well developed within 40 min and which may therefore be presumed to be due to direct action. However, extracts of leucocyte-free burned skin from animals pretreated with nitrogen mustard will also cause immediate leucocyte emigration It is clear, therefore, that leucocytes are not the only source of such a substance. In fact similar properties develop in serum after incubation with a variety of minced tissues, including quantities of leucocytes too small to yield a leucocyte emigration factor by themselves. Serum so treated also increases capillary permeability, but, by fractionation of such incubated serum, it is possible to separate a large part of the protein that causes leucocyte emigration from the major source of increased capillary permeability to protein These results suggest that leucocyte emigration, at least in sterile acute inflammation, may follow an enzymic reaction between plasma protein and the constituents of certain cells, *including* leucocytes themselves The mode of action of the factor is obscure. Chemotaxis cannot yet be confidently excluded, but a direct effect on the cells seems more likely, possibly an enzymic attack on some readily resynthesized component of the capillary wall (Hurley and Spector, 1961).

ACUTE RHEUMATIC FEVER[5]

The example of acute inflammation of most interest to cardiologists is rheumatic fever. Here, the injurious stimulus is the hemolytic streptococcus, and the tissue response is due to either an antigen-antibody reaction or special characteristics of the components of the streptococcus. Acute rheumatic fever is initially *exudative*, i.e., characterized by the formation of an inflammatory exudate consisting of the fluid constituents of the blood and of polymorph leucocytes. This stage of the disease is one of typical acute inflammation, and is associated with increased capillary permeability to protein (giving rise to fibrinous deposition, e.g., on the pericardium) and with leucocyte emigration. The process gives rise to *pericarditis, acute polyarthritis,* and probably similar damage in the myocardium and endocardium.

The exudative stage of acute rheumatism could well be due to the operation of the endogenous chemical mediators described above. Thus, an initial release of histamine would be followed rapidly by local destruction of arterenol and by activation of plasma protease-esterase systems and of permeability-increasing globulin, with formation of kinins. It is possible that some of the beneficial effects of *salicylate* in this stage of rheumatism are due to suppression of the enzyme reactions leading to the formation of kinins.

As an alternative, antigen-antibody combinations on the surface of vascular endothelium might alter capillary permeability without the intervention of extravascular endogenous substances. This might be achieved by activation of enzymes situated in the endothelium themselves and capable of modifying the permeability of the cells. At the moment, however, although much evidence has been accumulated in favor of the operation of chemical mediators of increased capillary permeability, there is no real evidence to support the alternative hypothesis. *Salicylates, however, could well work in acute rheumatic fever by a direct effect on the capillary wall, perhaps by inhibiting the hypothetical enzyme whose activation leads to increased permeability.*

The exudative stage of acute rheumatism is soon followed by the *proliferative stage,* the two processes often being present simultaneously in different tissues or parts of an organ. The major manifestation of the proliferative phase is the formation of the *Aschoff body.* This is a small paravascular collection of inflammatory cells with a center of necrotic connective tissue and polymerized fibrinogen; it consists essentially of two cell types. These are macrophages and modified macrophages on the one hand and antibody cells, i.e., lymphocytes and plasma cells, on the other. The presence of cells of these two broad categories is a feature of all similar granulomas, including tuberculosis and syphilis. These inflammatory cells are later joined by fibroblasts, which lay down fibrils of collagen that eventually replace the Aschoff nodule.

The accumulation of macrophages, plasma cells, etc., has not yet been shown to be due to a specific endogenous mechanism. It seems that they constitute a *response to injurious stimuli* that do not possess the power to cause increased capillary permeability and migration of polymorphs.

CAPILLARY PERMEABILITY AND SHOCK[6]

Shock is a state of peripheral circulatory collapse due essentially to a discrepancy between the circulating blood volume and the capacity of the peripheral vessels. It can arise as a consequence of a rapid reduction in blood volume or of profound vasodilatation, or both. The manifestations of shock are in part direct consequences of these changes and in part the result of the homeostatic mechanisms that they bring into play. In this latter category come such phenomena as vasoconstriction in organs such as the kidney or skin whose function is not immediately necessary to maintain life.

A common precipitating factor in shock is *sudden reduction in the volume of circulating blood.* This may occur as a result of massive acute hemorrhage. It also commonly follows severe loss of plasma into injured tissues, e.g., in extensive burns or crushing injuries of the limbs. In these circumstances, increased capillary permeability to plasma protein in the

[5] See Part 7, Chap. 2. Editor.

[6] See Part 14, Chap. 4. *Editor.*

damaged area as a result of injury is the major factor, although local hemorrhage due to physical destruction of vessels may play a part. Hemorrhage apart, these local changes differ in no important respect from those described as acute inflammation. Because of extensive destruction of tissue, however, large areas may be without adequate circulation of blood, and here the full picture of inflammation will not develop, this being reserved for the less severely affected regions at the periphery of the zone of damage.

With proper treatment of the local injury, most patients in shock respond to replacement of blood or plasma loss. In some instances, however, such therapy is unsuccessful. In these patients with irreversible shock, a variety of metabolic, toxic, and endocrine factors are involved, and the condition is the subject of much controversy It is established, however, that some of these patients (and also experimental animals in a similar condition) show *a paralytic dilatation of the small blood vessels in parts of the body far removed from the local injury*. The bowel and liver may be particularly involved. One of the essential changes is an inability of these vessels to react to vasoconstrictor amines, such as arterenol This phenomenon may be due to overstimulation by such amines in the earlier stages of shock or to the prolonged action of vasodilators, such as histamine These two situations may be related by virtue of the ability of arterenol to cause increased synthesis of histamine (Schayer, 1960). Other possible mechanisms for the paralytic dilatation of peripheral vessels in shock are absorption of bacterial toxins from a bowel partially devitalized by ischemia, and depressed activity of the reticuloendothelial system This last phenomenon might operate in a number of ways, including failure to remove bacterial toxin from the circulation. It is also possible that depressed activity of reticuloendothelial cells might be accompanied by a similar alteration in the properties of vascular endothelium, with resultant paralytic vasodilatation. Finally, there is the possibility of absorption of endogenous toxic substances, such as tissue polysaccharides, some of which share the harmful characteristics of bacterial endotoxin. It must be stressed that paralytic vasodilatation in shock is not normally accompanied by a parallel increase in capillary permeability, this change occurring only at the site of local injury.

CAPILLARY PERMEABILITY IN HEART FAILURE[7]

Edema is one of the cardinal manifestations of cardiac failure. However, this symptom is not due to increased capillary permeability, as can be seen from the low protein concentration (usually less than 0 1 per cent) of the extravascular collections of fluid. Edema due to increased capillary permeability, as in inflammation, exhibits a protein concentration of 2 to 6 per cent. The formation of edema in cardiac failure is a more complicated process and involves raised filtration pressure in the microcirculation (due to venous congestion), changes in blood volume, and abnormal retention of sodium in the tissues, usually because of diminished excretion, itself the outcome of a complex series of changes. These phenomena are of course beyond the scope of this article.

CAPILLARY PERMEABILITY IN PULMONARY EDEMA[8]

Edema of the lungs, as in other organs, may be due to one of three abnormalities· increased capillary permeability to protein, increased intracapillary filtration pressure, or decreased colloid osmotic pressure of the lung (Cameron, 1948). In practice, the last-named disturbance is unimportant as a cause of pulmonary edema, except as part of a body-wide accumulation of water.

The problem of pulmonary edema is rendered complex by the curious clinical abnormalities and experimental measures that lead to its appearance. For the purposes of the present discussion, the causes fall into four admittedly arbitrary categories—inhalation of irritants, systemic poisons, circulatory failure, and lesions of the central nervous system In all these groups, the pathogenesis of the edema, including the possible role of increased capillary permeability, is a subject of controversy.

There is on the whole rather less dispute concerning the nature of the pulmonary edema following inhalation of irritants such as phosgene, ketene, lewisite, and mustard gas Direct measurement of the protein content of

[7] See Part 18, Chap 4 *Editor*

[8] See also Part 18, Chap. 13 *Editor.*

the edema fluid, the rapid leakage of protein-bound dyes into the air spaces, and histologic examination of the pulmonary capillary endothelium, all *indicate damage to the pulmonary vessels and resultant increased permeability to plasma protein.*

It would seem reasonable to attribute this leakage of protein-rich fluid to a direct effect of the irritant gas on the vessel wall. There is, however, *some* indirect evidence that exposure to these substances leads to the *release in the lung of vasoactive compounds* that might be responsible for increased permeability in the pulmonary vessels. Thus, after exposure to *phosgene*, there is a latent period, both in man and animals, before edema sets in Furthermore, signs of *histamine release* may be apparent during this period Thus, guinea pigs develop bronchospasm, and dogs, circulatory collapse after phosgene (Cameron, 1948) These responses are characteristic of *massive* histamine release in these two species Finally, much of the pulmonary edema due to irritant gases is normally uncomplicated by hemorrhage In addition, the vascular changes are potentially reversible in a short space of time if the animal or patient survives These *facts suggest that* physical destruction of alveolar capillaries *is not* a prominent feature This *conclusion* in turn supports the view that exposure *to irritant gases* increases capillary permeability by causing the release within the lung of *endogenous* substances possessing this property

There is little information concerning the nature of *any such* compounds released in pulmonary edema Irritation of the pleura by *turpentine*, however, probably causes increased capillary permeability by an initial release of histamine followed by activation of a globulin-protease-esterase-peptide system It may well be that a similar mechanism is operative when the intrapulmonary capillaries are subject to chemical irritation

A large number of systemically administered chemical substances, of the most diverse types, *lead specifically* to the development of massive pulmonary *edema* The list includes methyl salicylate, *adrenalin* (epinephrine), alloxan, ammonium salts, and the thioureas (e g, anaphylthiourea, *ANTU*) (Visscher et al, 1956)

In the case of *ANTU*, there is some evidence for an increase in capillary permeability to protein, since this substance will produce edema in the isolated lung perfused at zero outflow pressure and at an inflow pressure below the colloid osmotic pressure of the blood On the other hand, after administration of *ammonium salts*, the pulmonary edema fluid contains little or no plasma protein, suggesting normal capillary permeability. This observation is supported by the findings of Sarnoff and Kaufman that there is a sharp rise in left atrial pressure in this condition, indicating that the cause of the edema is raised filtration pressure in the lung capillaries. The effect of ammonium ions on blood pressure may be mediated via *the sympathetic nervous system.*

The effect of *alloxan* appears to be different, in that left atrial pressure does *not rise* while there is pulmonary arteriolar constriction followed by dilatation of the capillaries with rise in filtration pressure. Capillary dilatation could be due to constriction of venules, but it is clear that there is little *evidence* of increased capillary permeability.

The pulmonary edema due to *epinephrine* is one of the most closely studied examples of the condition. There is a great deal of evidence to suggest that this edema is due to increased filtration pressure in the lung capillaries. This change appears to follow a massive diversion of blood from the systemic to the pulmonary circulation, associated with systemic hypertension, a rise in left atrial pressure, and the inability of the left *ventricle to* compensate for the altered hemodynamics. In spite of the weighty evidence indicating a hydrostatic origin of the edema with *no need* to involve altered capillary permeability, the edema fluid in such cases has been found to have a high protein content (Cameron, 1948).

In the case of pulmonary edema *due to lesion of the central nervous system*, a similar situation exists Thus, although the edema fluid, as sampled from the main bronchi, has on occasion been found to possess a high protein content, there *is much evidence* suggesting a hydrostatic *origin for the edema* Sarnoff has shown that neurogenic pulmonary edema is associated with a *rise in the* arterial and venous pressures of both *systemic* and pulmonary circulations Increased pulmonary capillary filtration pressure seems certain to follow

these changes. The alterations in pressure once again follow a shift of blood from the systemic to the pulmonary circuit.

The point now arises whether increased hydrostatic pressure in the pulmonary capillaries is in itself sufficient to cause edema or whether the circulatory changes described lead also to increased capillary permeability. The finding of high protein concentrations in the edema fluid in such cases is in itself sufficient reason to consider this question

Nervous stimuli are clearly important in the pathogenesis of many types of pulmonary edema including those due to lesion of the central nervous system and to chemical substances, notably epinephrine. The work of Wolff shows that nervous stimuli can cause increased capillary permeability, or at least greatly reduce the intensity of injury necessary to initiate this change.

The second point is that increased hydrostatic pressure in the capillaries may itself lead to increased passage of plasma protein into the extravascular space, particularly perhaps in the lung (Visscher et al., 1956). This abnormality is unlikely to develop at pressures of less than 40 mm Hg, which is many times the normal value. Moreover, the transudates so formed would appear to contain protein not in excess of 1 per cent, as opposed to values of up to 6 to 7 per cent in inflammatory exudates. The increased loss of protein with raised pressure is an experimental fact that is not easily reconcilable with theories of protein exchange through the capillaries based on the concept of restricted diffusion (Pappenheimer, 1953). The finding is more compatible with a theory of protein exchange based partly on filtration, or with the view that *distention of capillaries damages the integrity of their walls.*

It can be seen from this brief survey that the subject of capillary permeability in pulmonary edema is difficult and controversial. Two advances seem desirable in the elucidation of this problem; electron microscopy of lung capillaries in different types of edema to detect the changes characteristic of increased permeability (Alksne, 1959), and direct measurement of the protein content of the fluid in the alveolar spaces as opposed to the major bronchi.

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The regulation of blood volume

JAMES W. PEARCE

There is now ample evidence from experiments in man, as well as in other animals, of a complex mechanism for regulation of the volume of circulating fluid in the body This regulation manifests itself most obviously in changes of renal excretion of water and electrolytes, which tend to correct variations in blood volume The *interstitial fluid volume,* separated from the intravascular space by a porous capillary wall, will normally be subject to the same influences as the *blood volume,* both initial and corrective In the normal animal, exchange and distribution of fluid between the two compartments (intravascular and interstitial) of the *extracellular fluid space* are chiefly determined by hydrostatic and colloid osmotic pressure differences, and by capillary permeability These latter factors can be grossly altered by disease but can play no active role in governing the *over-all volume* of extracellular fluid

The regulation of intravascular volume is the major concern of this presentation, but it must be remembered that in disease and in certain artificial states, regulation of interstitial fluid volume may be dissociated from that of blood volume The body is also provided with a separate mechanism, elucidated by the work of Verney, for the regulation of the solute concentration of the extracellular fluid (*osmoregulation*) Upon the efficient operation of this mechanism, achieving constancy of osmotic pressure of extracellular fluid, depends the *intracellular* volume, the remaining compartment of body fluid. Under many circumstances, the regulations of osmotic pressure and volume will complement one another, either concomitantly or sequentially. As an example, one may visualize the sequence of events following *water loading* as a reduction in plasma osmotic pressure causing osmoreceptors in the anterior hypothalamus to reduce the secretion of antidiuretic hormone via the posterior pituitary gland, thus leading to a reduced renal tubular reabsorption of water and a consequent diuresis. This renal response corrects both the reduced osmotic pressure and the increased volume The opposite situation, *ingestion of a strongly hypertonic solution,* leads to a retention of water by the kidney and to increased water intake, which, although effective in returning osmotic pressure to normal, do so by enlarging extracellular fluid volume This volume increase, like that produced by ingestion or infusion of isotonic solution (and, on the other hand, the volume decrease following *hemorrhage*), is, in fact, followed by other appropriate renal responses, which operate to restore normal volume If the two regulations must oppose one another, as in *salt depletion,* isotonicity may be sacrificed in order to preserve volume, and then the intracellular fluid volume will be passively involved The *edema* of circulatory failure is an example of paradoxical disorder of normal regulation that is not yet fully understood, but it will be proposed here that slightly different mechanisms operate to control the filling vol-

ume of the lesser and greater circulations and that when they are called upon to oppose one another on a background of disturbed tonicity, the final combination of effects is indeed difficult to predict.

Although Starling around the beginning of the century postulated the existence of a regulation of blood volume, and the concept was strongly supported later by Peters and Borst, acceptance of a classical reflex mechanism to regulate blood volume has been delayed because of reliance on the simpler view that increased blood volume must lead to increased renal blood flow and hence to greater renal output. An automatic regulating device would thus be provided. The evidence is commonplace, however, that glomerular filtration rate does not necessarily vary with either renal blood flow or blood pressure. Even admitting the probability that tubular reabsorption may be influenced by renal hemodynamic changes affecting the concentrating mechanism, the evidence that *extrarenal factors* are involved is now overwhelming. The reader is referred to the comprehensive review by Smith of the evidence supporting this conclusion. In the present examination of the reflex mechanism for regulating blood volume, the approach will be a search for the classical components, a sensory limb to register volume, integrating and effector centers, and finally the effector systems operating to restore to normal the signals from the sensing device.

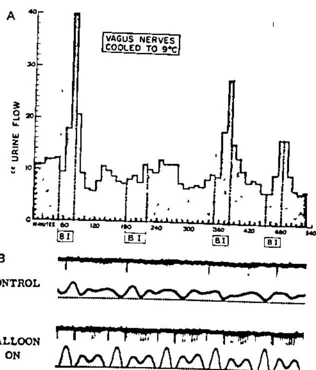


Fig. 2-99. A. Diuretic response in the anesthetized dog following distention (B I.) of a balloon in the left atrium is prevented by cooling the vagus nerves B. The activity of vagal fibers arising in left atrial stretch receptors is shown before and during balloon distention *Top*, electroneurogram; *center*, left atrial pressure; *bottom*, time marking at 60 cps. Conduction in such fibers was shown to be blocked between 12 and 6°C. (*After Henry and Pearce, by permission of the J. Physiol.*)

THE VOLUME RECEPTORS

Nervous receptors that could be expected to respond to changes in filling volume of the cardiovascular system might be located in the low-pressure circulation or in the high-pressure circulation One of the early pieces of evidence pointing to a thoracic location of volume receptors was the report (Strauss et al) that ingestion of 2,000 ml normal saline solution was followed by a prompt diuresis *only if subjects were recumbent;* subjects who remained upright retained the saline load over many hours It was concluded that the shift of blood volume toward the thorax, on lying down, stimulated receptors there which initiated the renal response Gauer and coworkers (1954), during a study of negative-pressure breathing in the dog, noted that a moderate diuresis usually accompanied the procedure, one which is known to shift blood from the peripheral vasculature into the thoracic viscera Reasoning that the responsible thoracic receptors should be found in the most distensible portion of the cardiovascular system, the low-pressure side, Henry and collaborators performed experiments in which *distention of a balloon in the left atrium led to a prompt and large diuresis* This renal response could not be evoked by pulmonary vascular engorgement achieved by constriction of the pulmonary veins, a maneuver which could be expected to produce similar effects on the greater circulation. The diuretic responses to both negative-pressure breathing and left atrial distention were usually prevented or much reduced by cold block of the vagus nerves (Fig 2-99A). It was later shown that left atrial stretch receptors, the vagal fibers of which were studied electrophysiologically, did respond in the dog with strikingly increased activity during balloon distention of

the atrium (Fig. 2-99B) but responded with only a modest increase in discharge during negative-pressure breathing. The evoked diureses consisted of increases in water output without consistent alteration in electrolyte excretion, a feature also of the diuretic response to similar negative-pressure breathing in the human subject. A comparable renal response has recently been reported (Currie et al.) to follow a variety of respiratory maneuvers, including carbon dioxide inhalation, the common effect of which was an exaggerated fluctuation of intrathoracic pressure. Atrial stretch receptors, which have also been found in the monkey, an upright primate like man, do then appear to provide at least one set of "volume receptors" responsible for reflex changes in urine volume seen to follow increase of intravascular volume.

If atrial receptors constituted the only volume receptors, section of the vagus nerves should prevent the renal response to physiologic expansion of the blood volume resulting from infusion into the circulation of isotonic plasma substitutes and of whole blood. Such was not the case in the experiments of Atkins and this author, where vagotomy usually reduced, but failed to prevent, the diuretic response of dogs to infusions of bovine albumin solution in saline or of plasma. These renal responses, like those described earlier in human subjects (Welt et al.), included a natriuretic component not seen when the volume expansion was limited to the thoracic viscera. Hence other receptors, in addition to those in the cardiac chambers, had to be involved.

Other regions of the low-pressure circulatory system seemed unlikely sites for these additional receptors, as engorgement of the limb veins, cephalic veins, and abdominal veins has in each case been shown to reduce urine flow or electrolyte excretion or both. Borst and Epstein have considered that receptors in the high-pressure circulation must contribute to the regulation of blood volume, and Borst and collaborators have summarized a variety of evidence from clinical studies relating "filling of the arterial system" to renal excretion of water and electrolytes.

Although combined denervation of the carotid sinuses and vagotomy have also failed to prevent the diuretic and natriuretic response to infusion of bovine albumin solution, Bartter and coworkers have recently reported experiments that clearly implicate a third buffer nerve, the common carotid nerve, in the regulation of urinary sodium output. This nerve arises in an arterial pressoreceptor zone near the origin of the thyroid artery from the common carotid, and, as it joins the nodose ganglion of the vagus, it could escape the combined denervation procedures described above. Bartter's experiments show that reduced stimulation of the common carotid pressoreceptors, which could result from a fall in either mean arterial pressure or pulse pressure, leads to an increase in secretion of aldosterone and a consequent decrease in urinary sodium output. Although changes in mean arterial pressure associated with alterations in cardiac output following physiologic changes in blood volume are neither large nor sustained (because of the regulation of vasomotor activity, which is the primary function of the pressoreceptors), variations in pulse pressure do persist. The implications of Bartter's findings in the regulation of aldosterone secretion in congestive failure, where the cardiac output is usually reduced and hence also the pulse pressure, will be referred to later.

Further experiments in the dog also showed that the rise in secretion of aldosterone which followed constriction of the inferior vena cava, a maneuver which would not only reduce the cardiac output but also deprive the thoracic viscera of normal filling volume, did not depend on the integrity of the vagus nerves. The return to normal of the aldosterone level following release of the constriction did, however, depend on the presence of intact vagus nerves. Although it is difficult at present to assess the effect of the tachycardia of vagotomy on the arterial pulse pressure, these observations, associated with those of Anderson and coworkers proving that mechanical stretching of the right atrium resulted in a lowered aldosterone secretion, suggest the following concept. The receptors of the high-pressure system appear to initiate the liberation of increased quantities of aldosterone in response to a decreased pulse pressure, a reflection primarily of stroke cardiac output. On the other hand, the receptors of the low-pressure system, while not concerned in the stimulation of in-

creased aldosterone output, appear to participate at least in the reduction back to normal of an elevated rate of secretion when normal thoracic blood volume is restored, or to reduce the rate of secretion below normal if thoracic blood volume is excessive. Such an interpretation would be consistent also with the finding that vagotomy alone does not lead to an increase in aldosterone output. This concept must be held as tentative, however, as the evidence for such an unorthodox "on-off" mechanism is still far from complete, and cold block of the vagi has also been shown to reduce aldosterone secretion below normal.

Assuming that volume-regulating receptors exist in both the low- and high-pressure sides of the cardiovascular system, need the search be extended for receptors of interstitial fluid volume? This question has been dealt with extensively by Grossman, and only a few pieces of evidence will be mentioned here which support an affirmative answer. Although it is difficult experimentally to change the interstitial fluid volume without simultaneously altering the circulating blood volume, changes in opposing directions may be achieved by grossly altering the colloid osmotic pressure of the plasma Welt and coworkers, and, later, Fine and his group have shown that increase in intravascular volume at the expense of interstitial fluid volume, produced by infusion of hyperoncotic albumin solution, will lower urinary sodium output or fail to correct a raised aldosterone level previously produced by hemorrhage Hence, in spite of increased blood volume, reduction of interstitial fluid volume, presumably without change in sodium concentration, can result in compensating urinary sodium retention. There are now indications that the midbrain plays a controlling role in regulating sodium output, and it is conceivable that nervous receptors exist that register changes in the degree of separation of cells There is no clear evidence at present pointing to the location of such receptors.

EFFECTOR MECHANISMS

Changes in circulating blood volume that lead to changes in vascular pressures must, by the classical Starling-Landis mechanism, be *reflected in* alterations in the same direction in capillary ultrafiltration. In addition to this passive phenomenon, neural control of precapillary resistance vessels, which according to Mellander can markedly alter the filtration gradient, may constitute an active part of the response. The fluid movement can amount to appreciable quantities, as evidenced by the hemodilution that follows moderate hemorrhage, and by the concentration of plasma protein that follows infusion of autologous plasma. Coupled with this passive mechanism is the reflex adjustment of vascular capacity that follows detection of arterial pressure fluctuations by the pressoreceptors and possibly also detection of altered filling volume by atrial stretch receptors. These two responses provide immediate buffering of abrupt changes in blood volume.

A secondary line of defense, provided by the kidney, consists of alteration of water and electrolyte output (Fig. 2-100). It is now clear that variation in the rate of secretion of *antidiuretic hormone* at least contributes to the increased water excretion seen following the infusion of isotonic bovine albumin solution, during negative-pressure breathing and atrial balloon distention in dogs, and to the decreased water excretion following orthostasis and hemorrhage Although it is a common finding that the glomerular filtration rate does not rise in response to increase in extracellular fluid volume (thus relegating the renal response to a tubular mechanism), moderate hemorrhage is usually associated with reduction in glomerular filtration, which can explain part of the reduced renal output of water

It has been clearly shown that *urinary sodium output decreases following hemorrhage* with reduction of extracellular fluid volume without change in serum sodium concentration, and orthostasis During these circumstances, it has been found, however, that the glomerular filtration rate does not change or else increases, and that a decreased filtration rate, when observed, does not account for the reduction in sodium output. Increased urinary sodium excretion has been *demonstrated following* infusions of bovine albumin in man and of either bovine albumin solution or plasma in the dog, and following expansion of the extracellular fluid volume in man, even with a lowered plasma sodium concentration. Again, these changes in *sodium*

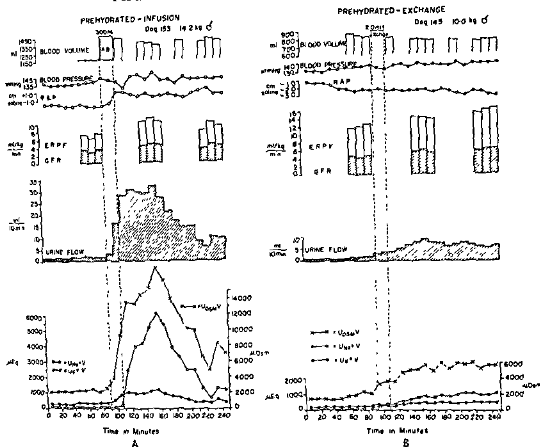


Fig 2-100. A Renal response in the anesthetized dog to expansion of the blood volume with an infusion of artificial blood (washed red cells suspended in a solution of 6 per cent albumin in saline solution) The infusion is largely retained and produces a modest rise in right atrial pressure (R A P) Note the pronounced increases in urine flow and total solute output ($U_{osm}V$), the latter largely due to natriuresis E R P F = effective renal plasma flow, G F.R = glomerular filtration rate B Renal response to procedures identical to those used in A, except that the infusion was exchanged for the animal's own blood, thus eliminating any increase in blood volume. Note the minimal increases in water and solute output despite comparable changes in renal hemodynamics Increase in extracellular fluid volume must, then, be responsible for compensating changes in renal tubular reabsorption (After Sonnenberg)

output can be completely accounted for only by decreased tubular *reabsorption*

Since methods of assay of aldosterone levels in the urine became available, attention has been focused on the level of this *steroid* as the important extrarenal factor *governing sodium* output. The evidence has accumulated that hemorrhage does indeed *increase aldosterone* output, as do reduction in total extracellular fluid volume, orthostasis, and reduction in thoracic blood volume produced by constriction of the inferior vena cava The early evidence that aldosterone output is *decreased* by increased central blood volume was based on somewhat unnatural alterations in the circulatory systems of dogs, but the recent studies of Bartter and coworkers, using infusions of albumin solution in man, have established this point A prompt fall in urinary aldosterone output has also been reported to follow *recumbency* in man, and miscellaneous infusions in unanesthetized dogs have resulted in markedly reduced levels of aldosterone in peripheral blood within 20 min (Bojesen et al).

Exception must be taken, *however*, to the acceptance of an exclusive role of aldosterone *in governing* the renal output of sodium in normal blood volume regulation Variations in *urinary* sodium output produced by ortho*stasis or other* maneuvers designed to shift the

circulating blood volume, and shown to be the result of altered tubular reabsorption, have been observed in patients with Addison's disease. *Natriuresis* following plasma infusion has been reported in adrenalectomized dogs. While many findings affirm that aldosterone plays a role in blood volume regulation, it seems wise to speculate as well on other possible effector mechanisms provided to alter urinary sodium output.

The suggestion of the existence of a *natriuretic hormone* is not new but is strongly supported by recent work (Keeler). Lesions of the *lateral hypothalamus* of the rat resulted in a threefold increase in urinary sodium excretion, which was not prevented by renal denervation, hypophysectomy, or adrenalectomy These lesions also reversed the usual decrease in sodium output which followed reduction of the extracellular fluid volume by peritoneal dialysis with 25 per cent acacia solution

A *sodium-losing material* has also been reported in the urine of patients with congenital adrenal hyperplasia, this might explain the apparent refractoriness to continuous aldosterone administration of human subjects, in whom sodium and water retention ceases when a critical weight gain has resulted

A second alternative natriuretic mechanism that has been proposed is a *direct nervous control of tubular reabsorption*, but there appears to be no evidence of this that cannot also be explained on the basis of humoral factors now being revealed A third and more likely alternate mechanism depends on *intrarenal hemodynamic changes*, the effect of which must be reconsidered in the light of recent revisions in understanding of the renal tubular concentrating process (Gottschalk et al.). As the efficacy of the concentrating gradient, established in the renal medulla by the proposed countercurrent mechanism, must depend in part on the rate of blood flow through the medullary vessels, both urine volume and solute content could be influenced by either the distribution of renal blood flow or the absolute flow rate Such changes could still be dictated by extrarenal influences, including the innervation of kidney vasculature, or by circulating hormones to which kidney vessels are differentially sensitive. The possibility also exists that redistribution of intrarenal blood flow depends on the viscosity of the blood, although this is not likely to explain renal responses to simple translocation of circulating blood volume.

REFLEX CENTERS

Although the detailed pathways of visceral afferent nerves remain to be revealed, there is some histologic evidence that the sensory vagal nucleus (receiving impulses from cardiovascular receptors) has connections via the dorsal longitudinal bundle with the hypothalamic and posterior midbrain nuclei Vagal afferent impulses, probably from atrial stretch receptors, can vary the secretion of *antidiuretic hormone* by the cells of the anterior hypothalamic nuclei. Approximately the same region must include the pathways or centers for the natriuretic mechanism studied by Keeler. The work of Farrell and his associates implicates the posterior midbrain structures in the ultimate regulation of adrenosteroid secretion. Lesions placed centrally in the upper hindbrain increased the levels of plasma *aldosterone* in experimental animals, whereas lesions placed in the midbrain led to a decrease in aldosterone secretion.

Attention was then directed to *the pineal gland* as the possible source of a hormone which, released in response to stimulation from hypothalamic centers, might in turn govern adrenocortical output of aldosterone. Pinealectomy was found to decrease blood levels of aldosterone in dogs, and extracts of the pineal tissue were found to possess, in the acetone-soluble fraction, a powerful stimulating effect on aldosterone production The active material has been called *glomerulotropin* or *adrenoglomerulotropin*, as it acts on the zona glomerulosa of the adrenal gland More recent studies indicate that the pineal gland may act only as a storehouse for a principle elaborated by other structures: a trophic function of pineal extract has not been demonstrated in other species An increase in aldosterone output following hemorrhage has been shown in decapitated dogs (Davis et al., 1961), leading one to suspect that additional extracerebral controls over *aldosterone* secretion must exist.

Evidence (Biron et al.) is available that *angiotensin*, liberated by the kidney, has a profound stimulating effect on aldosterone release, but it is not yet clear whether this is a

direct effect. *It seems likely that the pineal gland plays a major role in governing aldosterone secretion* Probably, like the posterior pituitary gland, the pineal gland stores and releases a trophic hormone, responding to information from integrating centers in the posterior midbrain for the regulation of urinary sodium output. Furthermore, it is not difficult to postulate appropriate connections with pressoreceptor nerve endings in the medulla, only a few interneurons away.

INTEGRATION AND AN ATTEMPT AT RELATION OF BLOOD VOLUME TO EDEMA OF CARDIAC DISEASE

The mechanisms of extracellular fluid volume regulation for which there is now evidence (Pearce, 1961) are presented in Figs. 2-101 and 2-102. It is apparent that slightly different mechanisms operate to correct an increase in blood volume from those which correct a decrease. It is proposed *that one set of responses to increased blood volume protects the heart and low-pressure vascular system from overloading and that the other set of responses to decreased blood volume ensures an adequate arterial supply and consequent tissue fluid circulation.* The reduced cardiac output of the "forward-failing" heart, detected first as a reduced pulse pressure in the arterial system, would lead to increased aldosterone secretion and consequent salt retention. A subsequent overstimulation of the atrial receptors, due to venous congestion of "backward failure," should lead *to an* increased output of urinary water. The inhibit-

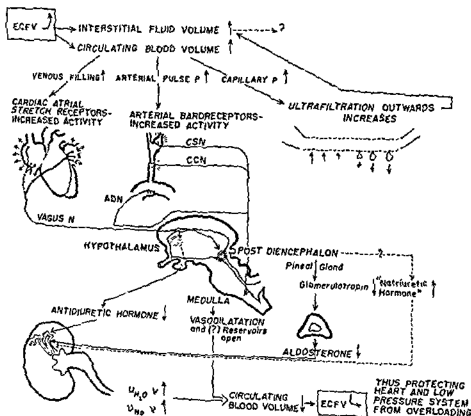


Fig 2-101 Diagram of proposed mechanisms by which an increase in extracellular fluid volume (ECFV) is counteracted Those features for which evidence is still only preliminary are indicated by small lettering or by interrupted pathways *ADN*, aortic depressor nerves, *CSN*, carotid sinus nerves, *CCN*, common carotid nerves; $U_{H_2O}V$ and $U_{Na}V$, total urinary water and sodium excretion. (Reproduced with permission of Brit Heart J.)

ing effect on antidiuretic hormone secretion is, however, not powerful (as seen in the modest diuresis which accompanies the atrial engorgement of negative-pressure breathing), and it might be unable to oppose the stronger stimulus to antidiuretic hormone secretion arising from retention of osmotically active sodium.

Although the atrial receptors do appear to influence electrolyte output during conditions leading to their prolonged overstimulation, again the powerful effect of reduced pressoreceptor activity might predominate in increasing aldosterone and antidiuretic hormone secretion. Finally, as has been stressed by others, isotonicity may be sacrificed in the efforts of the homeostatic mechanisms to maintain adequate circulation volume, leading to edema despite an accompanying hyponatremia. Only a *natriuretic hormone*, perhaps liberated in response to gross increase in interstitial fluid volume, would seem to be left to prevent unlimited and self-aggravating cardiac edema

Initial backward failure should lead to diuresis, because of stimulation of atrial receptors, with perhaps some reduction in aldosterone secretion if the stimulus is large enough to imitate the stretching maneuver of Farrell. Again, a persisting loss of water without proportionate loss of sodium defeats the mechanism by raising the extracellular fluid osmotic pressure. It seems that the moment the cardiac output began to decline (an unphysiologic consequence of raised venous pressure), the low-pressure side would be powerless to prevent salt and water retention. In experimental congestive failure, produced in dogs by circulatory obstruction (Davis et al., 1961), con-

REGULATION OF EXTRACELLULAR FLUID VOLUME (ECFV)

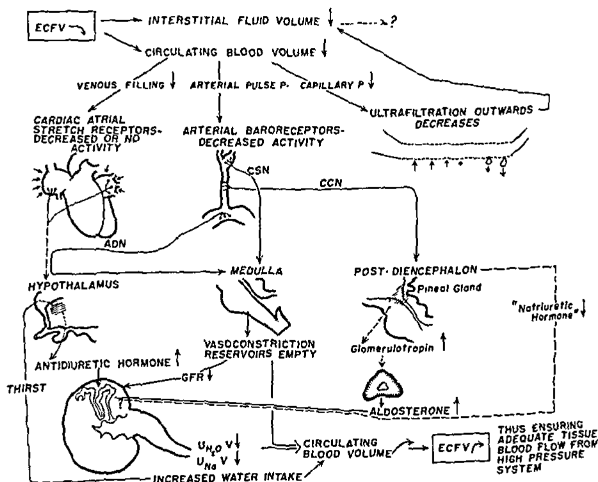


Fig. 2-102. Diagram of proposed mechanisms by which a decrease in extracellular fluid volume (ECFV) is counteracted Reservations and abbreviations are as in Fig. 2-101. (*Reproduced with permission of Brit. Heart J*)

striction of the inferior vena cava was much more effective in raising aldosterone secretion than constriction of the pulmonary artery. Assuming that the degree of reduction in cardiac output was similar in each case, it may be concluded that the engorgement of the right atrium at least mitigated the salt retention. Unfortunately, this is not borne out by the study of Wolff and associates, who found *greater elevation of aldosterone levels in the urine of patients with right-sided failure than in those with left-sided failure*. Other workers have not been able to find raised aldosterone levels in experimental congestive failure, even in the presence of edema caused by salt and water retention

The high levels of aldosterone seen with *hepatic cirrhosis* may be due to interference with the inactivation of the steroid by the liver, although this does not seem to be the explanation of the high aldosterone levels of *acute inferior vena cava constriction*, as they can be restored to normal by simultaneous infusion of blood into the supradiaphragmatic vasculature Further careful study of the cardiac output and arterial pulse pressure in relation to aldosterone levels during various stages of cardiac decompensation and recompensation may separate the role of the adrenal glands in maintaining cardiac edema from the role of other mechanisms

Other interesting hypotheses have been advanced to explain the edema of congestive failure Barger's suggestion that increased renal tubular reabsorption may be explained by an excessively high peritubular capillary oncotic pressure has received experimental as well as clinical support (Vander et al , Barger et al) Marked elevation of filtration fraction, due chiefly to fall in effective renal plasma flow, was found commonly in patients with edema of congestive failure and also developed, in association with inability to excrete a saline load, in dogs with experimentally induced failure of the right side of the heart The mechanism of this saline retention requires further examination in the light of newer concepts of the renal concentrating mechanism, but it was proposed that decreased pressoreceptor activity of forward failure could have been responsible for the reduced renal plasma flow. Most recently, Nelson and coworkers have suggested that an abnormal response to aldosterone may exist in patients with edema of various types, as they do not show the normal refractoriness to continued administration of excessive aldosterone. A relation between these findings and altered pineal secretion would be a revelation of great interest. It is unlikely that a single disorder of volume regulation will explain the features of cardiac edema.

CONCLUSIONS

In addition to the regulation of extracellular fluid osmotic pressure, the major factor determining intracellular volume, a complex mechanism exists for the regulation of extracellular fluid volume. The latter mechanism appears to depend upon sensory information from volume receptors in both the low-pressure and high-pressure sides of the circulation, and possibly also in the interstitial fluid compartment The volume of the extracellular compartment is adjusted first by changes in circulating blood volume, brought about by alterations in urinary water and electrolyte output. The low-pressure system receptors appear to regulate mainly the renal water output by varying the level of secreted antidiuretic hormone. Their function may be conceived as the protection of the low-pressure system and heart from overloading The high-pressure system receptors appear to regulate mainly the sodium output by varying the production of aldosterone, the parameter of pulse pressure, related to stroke cardiac output, is probably the relevant stimulus to volume regulation by these receptors, the function of which may be conceived as the maintenance of adequate tissue fluid circulation. An additional regulation of urinary sodium excretion must exist, and there is evidence supporting at least two possible mechanisms a natriuretic hormone, secreted in the midbrain, and a renal hemodynamic control of the tubular concentrating mechanism *The coordinating centers for the homeostasis of blood volume seem to lie in the midbrain, with the anterior hypothalamic centers controlling water output, and the posterior diencephalic centers (possibly including the pineal gland) controlling sodium output.*

The salt retention of cardiac decompensation can (in some cases only) be explained on the basis of reduced cardiac output leading to increased aldosterone secretion, in spite of

the overruled opposing influence from engorgement of the lesser circulation. An abnormally increased renal reabsorption of water and salt, due to a raised filtration fraction, or an enhanced sensitivity to aldosterone, may contribute to salt and water retention in states of edema. Although its disorder in disease is poorly understood, *the existence of a mechanism to regulate blood volume in the normal state must now be accepted among the homeostatic mechanisms designed "to maintain the constancy of the internal environment"*

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Functions of the pericardium

JOSÉ L. DUOMARCO, CYRO E. GIAMBRUNO, AND RICCARDO RIMINI

According to Wiggers (1944) as many as six functions have been attributed to the pericardium Only three of them are apparently beyond controversy fixation, gliding, and protection against cardiac dilatation The first two are normal, the latter appears under pathologic conditions

NORMAL FUNCTIONS OF THE PERICARDIUM

The pericardium is a strong membranous sac that fixes the position of the heart within the thorax In certain positions of the body, this normal function involves an important effort because the heart, an organ with a density similar to that of water, tends to fall toward the dependent portions of the pulmonary environment, which have a much lower density In this connection it is worth recalling that in the abdomen, where all the viscera are of about the same density, each viscus is supported by the hydrostatic action of the remaining viscera, for this reason, the visceral ligaments are weak and constitute mere anchors, which select one of an infinite number of possible positions (Duomarco and Rimini, 1947) The smoothness of the two pericardial layers permits rapid displacements of the heart during cardiac contraction The abnormal mobility of the heart deprived of the pericardium and its loss of mobility following the formation of *adhesions* of the serosa do not represent a serious handicap for the person with an average degree and type of physical activity. *Partial defects of the pericardium* are more likely to give rise to accidents in connection with vascular kinking (White, 1951).

ADAPTATION OF THE PERICARDIUM TO ITS CONTENTS

It is well known that the pericardial sac is poorly distensible when submitted to a sudden traction (Barnard, 1898), but that it does yield to a considerable extent to the continuous action of the heart if this organ becomes enlarged or changes in shape. This hard *plasticity* of the pericardium enables it to adapt to the shape and volume of the heart. This adaptation can hardly be conceived without the existence of an eccentric action of the heart upon its fibrous envelope. Available physiologic evidence, however, does not seem to point toward this direction Thus, the recording of the pressure of a gas or liquid distending the pericardium to varying degrees yields plethysmographic curves with negative systolic waves (Fig. 2-103A, B), which are unlikely to account for an enlargement of the pericardial cavity Conversely the terminal venous pressure sets up an eccentric, diastolic action, which may explain the adaptation of volume but not of shape Furthermore, this diastolic action includes the occurrence of venous hypertension prior to pericardial dilatation, an occurrence which, at least in a large number of cases, fails to be observed.

The tracings of *pericardial local pressures* by means of small balloons attached to the pericardial wall or introduced into its cavity reveal positive systolic waves of a shape similar to those produced by the underlying cardiac chamber (atrium or ventricle Fig 2-103C through G) This finding, together with the fact that, as a rule, the "pericardial systole" begins with the ejection phase, fol-

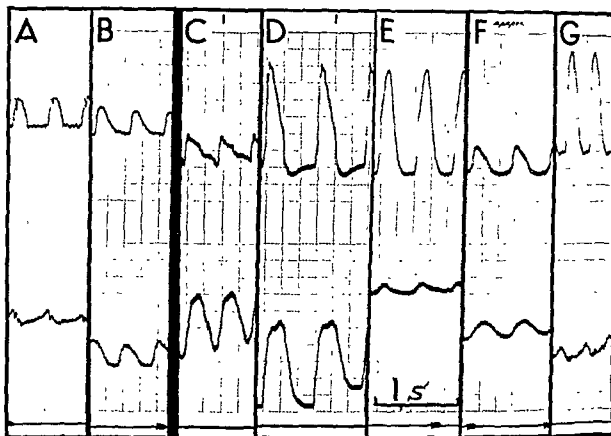


Fig. 2-103. Tracing of intracavitary pressure (top) and pericardial pressure (bottom) in dogs with open-thorax and artificial respiration. A. Right ventricular pressure and pressure of the pericardium distended with air, opposite course of both curves. B Same as in A, with the pericardium distended with fluid C Pressure of the pulmonary artery and local pressure of the undistended pericardium over the right ventricle; the direction of the systolic waves coincides from the beginning. D. Right ventricular pressure and local pressure upon the right ventricle; there is a slight delay in the initiation of the pericardial wave E. Right ventricular pressure and local pressure upon the infundibulum of the right ventricle. F Same as in E, over the infundibulum of the left ventricle. G. Same as in E, over the right atrium; the atrial wave precedes the ventricular.

lowing the tension period, suggests that *the local pressure of the heart upon the pericardium is due to the ballistic recoil of each cardiac chamber during ejection* These systolic actions cause the adaptation of the pericardium to the size and shape of the heart. On the other hand, the contents of the pericardium at the end of diastole tend to assume a spheral shape with a minimal surface Because of the ensuing ventricular systole, the heart undergoes a sudden change in shape, with a logical increase of cardiopericardial contact surface without a change in volume The increased surface, however, entails a rise in the potential capacity of the pericardium over the maximal volume of the heart in diastole. The cardiac systole, hence, not merely gives rise to the adaptation of shape and volume but also sets up the *reserve pericardial volume* (Duomarco, Giambruno, and Correa Durán, 1959).

LIMITING ACTION OF THE PERICARDIUM UPON HEART VOLUME

The possibility that the pericardium might exert a *protective function* against cardiac dilatation is only one aspect of the following broader question: Are there any circumstances in which the pericardium exerts a limiting action upon the volume at which the heart is working?

Under normal conditions, this occurrence was considered in the past a *definite fact*

during exertion, in the light of experimental evidence deriving from Starling's heart-lung preparation (Pickering, 1960). However, old roentgenologic data, as well as recent experiments by Rushmer (1959), tend to demonstrate that both man and animals, under normal conditions, do not react to increased physical exertion with an increase but rather with a decrease of cardiac volume.[1]

Under experimental conditions, a limiting action of the pericardium is observed (1) when its capacity is reduced (intrapericardial injection of saline solution, suture of wall), (2) when the cardiovascular system is distended (transfusion of blood or plasma substitutes) (Holt, Rhode, and Kines, 1960), (3) when the cardiac volume increases (increase of work, decrease of contractile energy, bradycardia).

The hemodynamic conditions of the ventricle having a limitation of its diastolic expansion can be seen in the tracing of Fig 2-104 In the normal cardiac cycle, there is a regular succession of systolic and diastolic waves, in the pathologic cycle of the "limited" heart, diastole is followed by a third period of *stagnation,* marked by a constant volume and a pressure that is above diastolic pressure During this truly "lost time," there is no progress of blood from either the heart to the arteries (as in systole) or from the veins to the heart (as in diastole), furthermore, there is no volumetric preparation of the heart for the subsequent systole The cardiac volume is found motionless between the *vis a tergo* and the elastic reaction of the heart at its maximum possible volume This hemodynamic condition is present not only in *pericardial constriction* but also when the dilated heart without pericardium works at the area of scarce distensibility or when the cardiac rate is sufficiently reduced Such a condition is the most genuine expression of cardiac failure and does not necessarily reflect a specific alteration of the myocardial fiber.[2]

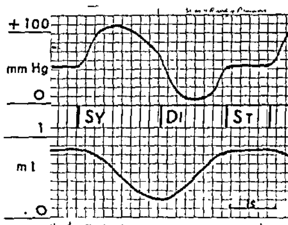


Fig 2-104. Tracing of pressure *(top)* and volume *(bottom)* of the isolated ventricle of toad working at a low rate in an inert circulatory system. Under these experimental conditions, the diastole *(Di)* was found to end before the next stimulation, and a period of ventricular stagnation *(St)* occurred

The following hemodynamic disturbances, described according to Kuno (1915), are mechanical consequences of the limiting action of the pericardium (1) increase of pulmonary and systemic venous pressures resulting from ventricular stagnation, (2) secondary decrease of cardiac output, (3) decrease of pulmonary and systemic arterial pressures, (4) increase of pulmonary and systemic vascular resistances, (5) shifting of blood from the arteriocapillary to the capillary-venous sector (increase of central blood volume), and (6) shift of blood from the systemic to the pulmonary circulation or vice versa (Fig 2-105).

The dilatation of one cardiac chamber may produce a limiting action of the pericardium over the entire heart Thus, Berglund, Sarnoff, and Isaacs (1955) demonstrated that experimental coarctation of the aorta in the dog causes an increase in the work of both ventricles, which decreases in the following order

[1] The above findings have erroneously been used to question the so-called "law of Starling" governing the adaptation of the heart to the circulatory needs of the body Actually at least three well-known adaptation mechanisms are at play in this process (1) Starling's mechanism, (2) changes of cardiac rate, (3) changes of myocardial contractility of neurohumoral origin One may readily concede the existence of a wide range of reciprocal substitutions while the denial of any of the foregoing mechanisms is hardly understandable

[2] The "dip" and the "plateau" of the intraventricular pressure curve in ventricular failure and in pericardial constriction as observed by Bloomfield and coworkers (1946) correspond, respectively, to the diastole and the stagnant period of the three-stage pathologic cycle reported by Duomarco (1947) in the isolated ventricle of the toad

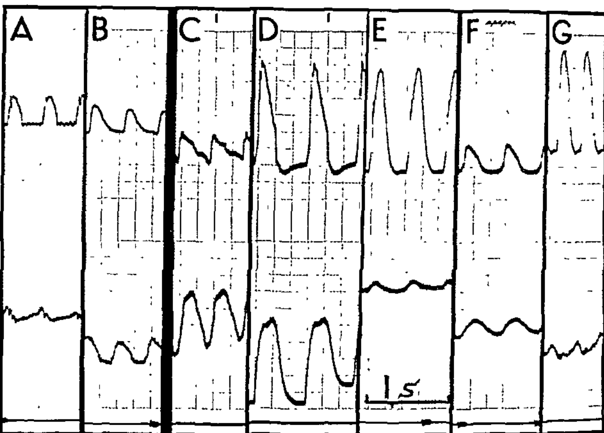


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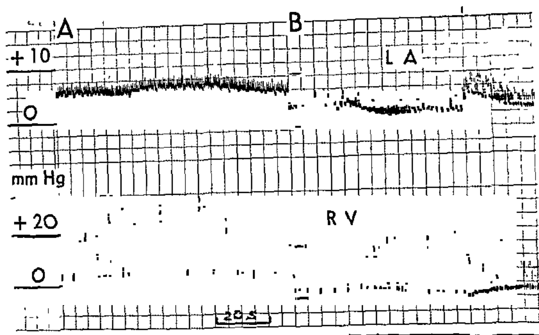


Fig 2-106. Effects of experimental coarctation of the pulmonary artery A. Progressive constriction of the pulmonary artery, with an intact pericardium, causes an increase of right ventricular (RV) and left atrial (LA) pressures B Opening of the pericardium reverses the effect in the left atrium.

pressure A number of arguments favor the theory of pericardial limitation. (1) In cases of *acute cardiac failure*, myocardial dilatation precedes pericardial adaptation (2) In the *absence of the pericardium* (for instance, in Starling's preparation), the failing heart is marked by severe ventricular (particularly right ventricular) dilatation, with insufficiency of the AV valves (particularly the tricuspid), and a marked enlargement of the atria (Lian, 1909, Winiwarter, 1931) Such a condition seldom occurs in man, and therefore the important part played by the pericardium in limiting cardiac dilatation becomes apparent (3) Regardless of the cause of limitation, its occurrence provokes a homeostatic reaction due to the effect of arterial hypotension on the carotid sinus, and marked by a hypervolemia, which in turn favors pericardial limitation

A related problem has to do with the frequent transformation of failure of one ventricle into bilateral ventricular failure (Luisada, 1932) When failure of one ventricle occurs, a rapid increase of the volume of the corresponding atrium rapidly follows, causing a secondary increase of the volume of either the pulmonary or the splanchnic blood volume These circumstances in turn determine a limiting action of the pericardium upon the heart, which reduces the work of all chambers and tends to cause complete heart failure, partly of pericardial origin

Myocardial limitation, continuous propagation, and the possibility of partial failure versus *pericardial limitation, contiguous propagation, and total failure* appear to be the alternatives of chronic cardiac insufficiency The second hypothesis seems more satisfactory

With the above in mind, it has been assumed (Table 2-15) that pericardial limitation and secondary hypervolemia are necessary conditions in chronic heart failure

Five of the most conspicuous parameters of circulatory dynamics are considered Value 0 has been given to all normal or slightly affected parameters. the simplest scale was adopted, such as would permit the expression of directional variations without quantitative claims In this connection, only two degrees have been ascribed to the limiting action and to hypervolemia, while due consideration is given to the fact that when the two causes act simultaneously, their order of ap-

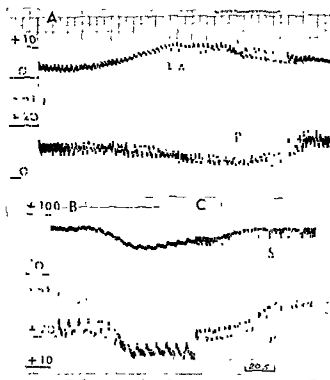


Fig. 2-105. Effects of pericardial distention with saline solution in the dog A Pericardial hypertension causes a rise of left atrial pressure and a decrease of pulmonary arterial pressure. B. Pericardial hypertension causes a drop of systemic and pulmonary arterial pressures. C Upon termination of the pericardial hypertension, systemic rise is faster than pulmonary rise, as a result of the greater collection of blood in the pulmonary circuit

of circumstances open pericardium, normal pericardium, constricted pericardium The left ventricle becomes dilated as a result of increased work, with consequent limitation of the diastole of the right ventricle, which in turn decreases the supply of blood to the left ventricle, and partially corrects the dilatation of this chamber

The limiting action of the pericardium may give rise to paradoxical pressure changes of the left atrium The above-quoted authors demonstrated that left atrial pressure increases following experimental aortic coarctation, but this rise is decreased by constriction of the pericardium (decreased output, an indirect effect, is more important than the direct effect of constriction). Duomarco and coworkers (1959) demonstrated that in the presence of pericardial constriction, increased blood volume, or both, coarctation of the pulmonary artery causes a rise of left atrial pressure (the direct effect of decreased output is exceeded by the indirect effect, i.e., the rise of intrapericardial pressure) (Fig. 2-106) In both instances, and from opposed positions, the pressures of both atria tend to become similar.

It is worth pointing out that aortic or pulmonary coarctation—unaccompanied by pericardial constriction or hypervolemia—does not necessarily cause this paradoxical behavior of the left atrium. This is explained by the fact that the increase of cardiac volume may be smaller than the reserve capacity of the pericardium.

Under pathologic conditions, a number of causes may determine the limiting action of the pericardium, any of them may affect more than one of the above three mechanisms. The limiting action of the pericardium is, of course, present when the space occupied by the heart is originally reduced (hydropericardium, constrictive pericarditis). It is also manifest in acute conditions, accompanied by a total or partial increase of heart volume (hypoxia, embolus of a large vessel, AV block) or of blood volume (blood transfusion, action of corticosteroids). As a rule, in any condition marked by rapid increase of venous pressure, the limiting action of the pericardium definitely plays a role, for it is unlikely that such an increase occurs without causing diastolic dilatation of the heart with complete filling of the pericardium The possibility that such a limiting action might occur in chronic cardiac conditions is dependent upon the relationship between the rate of cardiac enlargement and the adaptation capacity of the pericardium.

In *chronic congestive failure,* the limiting action of the pericardium becomes apparent. It has been stated that even when deprived of the pericardium, the failing heart is marked by a three-stage pathologic cycle (Fig. 2-104), the limiting action depends, in such case, upon the poor distensibility of the ventricle working at an excessive volume Since the insufficient heart has attained the above cycle, one may ask which is the first limiting factor, the pericardium or the myocardium itself working at the area of poor distensibility An experimental approach to the problem might be based on the fact that if the limitation is pericardial, the intrapericardial pressure ought to be high and close to the venous pressure at the end of ventricular diastole; on the other hand, if it is myocardial, it should be similar to pleural

pearance influences the direction of the values of arterial pressure and cardiac output. The circulatory apparatus has been conceived at first as an inert elastic system; later on, adjustments have been set forth in connection with well-known phenomena of vasomotor regulation.

The following deductions may be drawn (1) The addition of the parameters corresponding to a pure *hemodynamic condition*, plus pericardial limitation and secondary hypervolemic reaction, provide without additional hypotheses the basic hemodynamic characteristics of cardiac failure. (2) In every degree and form of cardiac failure, *and* in average cases of mitral stenosis, there is an increase of pulmonary and systemic venous pressures which is hard to explain with the theory of lineal propagation, but which is a logical consequence of pericardial limitation[3] (3) In accordance with available evidence, Table 2-15 *shows a decrease of output* in *mitral stenosis*, in the absence of right ventricular failure, a condition that would be necessary if the theory of continuous propagation is adopted. (4) The syndrome of *circulatory congestion* described by Eichna (1960) is easily explained as the result of pericardial limitation, in the course of highly varying circulatory conditions, *not necessarily accompanied by a myocardial* lesion.

[3] Duomarco, Rimini, and Sapriza (1950) have observed by means of angiocardiography in the upright position that in cases of slight left ventricular failure, the collapse of the superior vena cava disappears, this reveals an increase of central systemic venous pressure Experiments now in progress by means of cardiac catheterization have shown similar occurrences, especially in mitral stenosis, in which the pericardial limitation is of atrial origin

Certain differences between Table 2-15 and available clinical evidence have been "corrected" by means of signs (.) and (,), which *represent*, respectively, an increase and a decrease. Oddly enough, in the hemodynamic *conditions affected by* (.), *an increase of pulmonary vascular tone* has been demonstrated, which may explain the increase of pulmonary arterial pressure, not to be expected in an inert system (Shepherd and Wood, 1959; Selzer, 1959, Charms, Brofman, and Kohn, 1959) On the other hand, the decrease of output and *systemic pressure, as indicated* by (,), corresponds to the difference between an inert system and one affected by vascular reflexes of carotid origin (Fowler, Bloom, and Ward, 1958, Frye and Braunwald, 1960).

From a *clinical* and experimental standpoint it is, then, of interest that the clinical picture of cardiac failure is to a great extent the result of pericardial constriction or limitation, and therefore could be investigated in a relatively simple way

TABLE 2-15 EFFECT ON SYSTEMIC AND PULMONARY PRESSURE AND OUTPUT OF CERTAIN HEMODYNAMIC CONDITIONS, WITH CORRESPONDING CLINICAL CONDITIONS

	Classification of condition	*Hemodynamic condition*		*SVP*	*PAP*	*PVP*	*SAP*	*Output*	*Clinical condition*
1	I	Normal		0	0	0	0	0	
2	II	Compensated, nonobstructive cardiopathy		0	0	0	0	0	Valvular insufficiencies and myocardial conditions, compensated
3	III_1	Limiting action of pericardium	Intense	+ +	– –	+ +	– –	– –	Cardiac tamponade, acute pericarditis
4	III_2		Slight	+	–	+	–	–	
5	IV_1	Central or total hypervolemia	Intense	+ +	+ +	+ +	+ + ,	+ + ,	Compensated hypervolemia; blood transfusion; polycythemia, anemia, beriberi, action of corticoids [compensated hyperkinetic syndromes; hyperthyroidism, arteriovenous fistula; acute nephritis]
6	IV_2		Slight	+	+	+	+ ,	+ ,	
7	$III_1 + IV_2$	Limiting action + hypervolemia		+ + +	–	+ + +	–	–	Constrictive pericarditis, decompensated nonobstructive cardiopathies endomyocardial fibrosis [myxedema]
8	$IV_1 + III_2$	Hypervolemia + limiting action		+ + +	+	+ + +	+ ,	+ ,	Circulatory congestion: decompensated hypervolemias, decompensated hyperkinetic syndromes
9	V	Compensated circulatory obstruction	Systemic arterial	0	0	0	+ +	0	Arterial hypertension and aortic coarctation, compensated [aortic stenosis]
10	VI		Pulmonary arterial	0	+ +	0	0	0	Pulmonary hypertension, compensated [pulmonary stenosis]
11	VII		Mitral	0	+ +	+ +	0	0	Mild mitral stenosis
12	$V + III_1 + IV_2$	Decompensated circulatory obstruction	Systemic arterial	+ + +	– .	+ + +	+	–	Decompensated arterial hypertension
13	$VI + III_1 + IV_2$		Pulmonary arterial	+ + +	+	+ + +	–	–	Decompensated pulmonary stenosis
14	$VII + III_1 + IV_2$		Mitral	+ + +	+ .	+ + + + +	–	–	Average mitral stenosis

Note: *SVP* = Systemic venous pressure; *PAP* = pulmonary arterial pressure; *PVP* = pulmonary venous pressure; *SAP* = systemic arterial pressure; (.) (,) = positive and negative values due to pulmonary vasoconstriction and systemic vasodilatation, respectively; [ ] = partially related conditions

pathetic preganglionic cell bodies in the spinal cord.

c. *Efferent pathways* to the spinal cord. These include the possibility of direct outflow from each integrative level of the central nervous system to the spinal cord, rather than a primary outflow from the vasomotor area which is subject to supramedullary influences

Information in some of these areas has been obtained but there is serious deficiency of the specific evidence that is necessary for an understanding of cardiac regulation by the central nervous system. Neither has there been any attempt to synthesize into an organized schema the already existing knowledge It is no longer tenable to consider the over-all problem of central nervous control of the heart on the basis of cardioaccelerator and cardioinhibitory centers in the medulla, whose excitability is subject to modification by higher levels of the central nervous system

CARDIAC EFFECTS OF BULBAR STIMULATION

It has been known for many years that stimulation of various somatic afferent nerves results in reflex changes in heart rate (Hunt, 1899), and that these depend upon reciprocal inhibition between the centers controlling sympathetic and parasympathetic outflow to the heart (McDowall, 1938) Subsequent investigation of the carotid sinus and aortic arch pressoreceptor reflexes (Bronk et al, 1934, 1936, 1940, Heymans et al., 1958) elaborated on the reciprocal inhibition of these cardiac centers and provided evidence that *the acceleration of the heart is functionally associated with peripheral vasoconstriction* This eventually led to the conviction that there is also an anatomic juxtaposition of cardioaccelerator and vasoconstrictor areas in the medulla Few studies have been directed specifically toward the investigation of a medullary cardioaccelerator center Chen and associates (1937) reported a modest (15 per cent) increase in heart rate following sciatic nerve stimulation in a vagotomized, adrenalectomized, midbrain-transected dog. This is one of the few experiments with adequate control of experimental techniques that indicate some degree of medullary integration of cardioacceleration mediated by sympathetic pathways. Their procedures essentially ruled out such influences on heart rate as central vagal inhibition, secondary effects from adrenal medullary secretion, and the role of higher levels of the central nervous system. Using electrophysiologic techniques, Alexander (1946) demonstrated a significant reduction of electrical activity in the inferior cardiac nerve when a section was made through the rostral end of the medulla in decerebrate cats This was interpreted as a reduction in tonic cardioaccelerator activity. However, careful examination of his simultaneously recorded pressure pulses reveals no decrease in heart rate Thus, *the record of electrical activity in the cardiac nerve was indicative of some sympathetic outflow other than that affecting heart rate.*

Peiss (1958) reported no significant short-latency increase in heart rate following stimulation of the vasomotor area of the medulla in vagotomized animals under pentobarbital anesthesia. *Long-latency* cardiac acceleration was shown to be due to secretion of the adrenal medulla. In a later study (Peiss, 1960) it was shown that prompt cardioacceleration can be elicited from the vasomotor area if the animals are anesthetized *with chloralose* From previous evidence that pentobarbital depresses the excitability of hypothalamic structures mediating sympathetic responses, it was proposed that cardioacceleration elicited by medullary stimulation is the result of activation of afferent pathways to higher levels of the central nervous system, and that these pathways are blocked by pentobarbital

Figure 2-107 illustrates an experiment testing this specific point In A, B, and C of the figure, the stimulating electrode was located 1 mm below the floor of the fourth ventricle, 1.5 mm to the left of midline, and 2.5 mm rostral to the obex *A indicates the cardiovascular response to stimulation of this point in the vagotomized cat under chloralose anesthesia* Between A and B, a large electrolytic lesion was made in the brain stem at the level of the red nucleus. *B shows the results of restimulation in the medulla* Both the magnitude and time of onset of acceleration and augmentation were reduced significantly Between B and C the extent of the lesion was increased so that it involved almost complete destruction of

was almost ineffective in producing increased rate

5

Sympathetic control of the heart

Central Nervous Mechanisms

CLARENCE N. PEISS

Peripheral Mechanisms

WALTER C. RANDALL

CENTRAL NERVOUS MECHANISMS

Prevailing concepts of central nervous control of the heart are concerned primarily with the regulation of heart rate through reciprocally innervated cardioaccelerator (sympathetic) and cardioinhibitory (parasympathetic) centers It has been generally accepted that these centers are located in the medulla oblongata, in close functional and anatomic relationship to the vasomotor center. In large measure this concept has been derived from indirect evidence and from analogy with the more extensively investigated vasomotor mechanisms (Peiss, 1960) However, a comprehensive evaluation of the central nervous regulation of sympathetic outflow to the heart requires knowledge in the following areas.

1 The parameters of cardiac function that are subject to modification by neural activity. These include:

a Changes in heart rate mediated by increased or decreased activity in sympathetic fibers terminating in the area of the SA node Also involved are changes in conduction velocity of the cardiac impulse and more pronounced modifications in the electrocardiographic pattern, although the latter may not occur under normal physiologic activation and may have no regulatory significance.

b. Changes in contractility of myocardial fibers, the velocity of the contractile processes, and length-tension relationships in both atria and ventricles. These functional responses are discussed below under Peripheral Mechanisms.

c. Changes in coronary blood flow, which is subject to both sympathetic influences, directly exerted on the coronary blood vessels, and secondary influences produced by changes in heart rate, myocardial contractility, and metabolic rate.

2. The neuronal network involved in the regulatory mechanism. This includes:

a. Direct and indirect afferent pathways, which eventually terminate on cells that have a sympathetic outflow to the heart The most familiar examples of this afferent input are the classical presso- and chemoreceptors of the carotid sinus and aortic arch, although there is insufficient information concerning their role in regulation of the heart It is apparent from even a brief survey of the literature that a multitude of sensory inputs in some manner affects cardiovascular function and must therefore be integrated neurally into the regulatory mechanism.

b. Cells in several parts of the brain, which serve important integrative functions for the cardioregulatory mechanism. These integrative areas and the interneurons connecting them eventually determine the efferent output to the sym-

and subthalamus under proper conditions. These responses included peripheral vasoconstriction, cardioacceleration, and increased myocardial contractile force.

Figure 2-108 illustrates a response to electrical stimulation of the hypothalamus in a vagotomized dog under chloralose anesthesia. Within 2 sec of the onset of stimulation, heart rate, blood pressure, and force of ventricular contraction all began to rise. Eighteen seconds later, at the termination of stimulation, heart rate had increased from 150 to 215 per minute, blood pressure from 170/137 to 318/225 mm Hg, and the myocardial contractile force had approximately doubled.

It is readily apparent that this brief stimulation in the posterior hypothalamus resulted in a huge activation of the sympathetic outflow to the heart. It can be presumed that increased outflow to the peripheral blood vessels also occurred, because of the large increase in diastolic pressure. In some degree, but not entirely, the increase in diastolic pressure may be ascribed to the increased heart rate.

It has been shown (Randall et al., 1957) that peripheral outflow of accelerator and augmenter fibers to the heart is not equally distributed in the right and left sympathetic trunks. A relatively homolateral distribution of fibers also exists in the hypothalamus and brain stem of the dog, although the specific location of the tracts is not known.

In 9 of 14 dogs, a relatively greater change in myocardial contractile force was observed when the left side of the hypothalamus was stimulated. In all cases there were also moderate to large increases in heart rate. Stimulation of the right side of the hypothalamus produced greater cardioacceleration than stimulation of the left side in the same dog. At some points in the right side of the brain stem, a pure acceleration with no change in myocardial contractility was observed. Figure

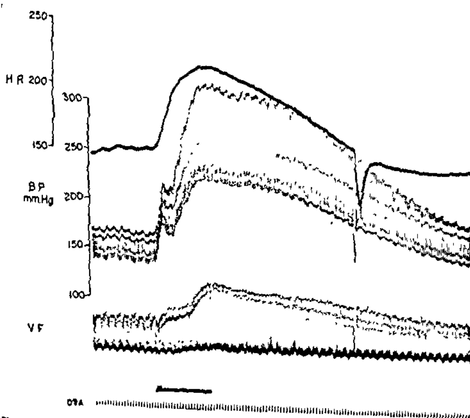


Fig. 2-108. Cardiovascular response to stimulation of the posterior hypothalamus in a vagotomized dog under chloralose anesthesia, showing changes in heart rate, systolic and diastolic pressure, and ventricular contractile force (VF). Solid bar indicates period of stimulation. Time line in 1-sec intervals.

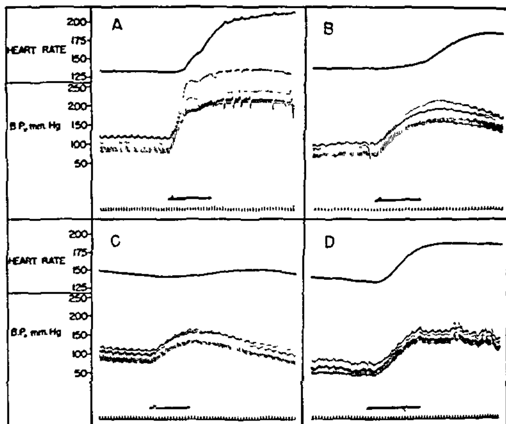


Fig. 2-107. Effect of lesions (just caudal to the hypothalamus) on cardioaccelerator response to stimulation of dorsal medulla (parts A, B, and C) in a vagotomized cat under chloralose anesthesia. A. Prelesion response. B Response after partial lesion. C. Response after more extensive lesion. *D. Response with electrode repositioned in ventrolateral medulla after above lesion.* All stimulations at 2.4 volts, 2 msec, and 70 cps. Solid bar indicates periods of stimulation. Time line in 1-sec intervals (*From Peiss, J Physiol.,* 1960)

and contractility of the heart In D, the electrode was moved to the ventrolateral medulla Stimulation resulted in a significant pressor and accelerator response, presumably by activation of hypothalamospinal pathways The prompt cardioacceleration indicates that the procedures performed in the experiment did not abolish the ability of peripheral mechanisms to respond to electrical activation

On the basis of this type of experiment it has been concluded that there is relatively little integration of sympathetic control of heart rate and myocardial contractility at the bulbar level. It has been shown that no more than 20 per cent of such responses elicited by stimulation of the medulla persist after interruption of the brain stem by midcollicular transections or by massive lesions just caudal to the hypothalamus Thus it appears that *the majority of functional cardiac responses produced by stimulation of the medulla is due to activation of afferent pathways to higher levels of the central nervous system, and that the integrative functions must occur at these higher levels.*

CARDIAC EFFECTS OF DIENCEPHALIC STIMULATION

Cardiovascular responses to stimulation of the hypothalamus were first described by Karplus and coworkers (1909, 1927). Detailed mapping of this area was reported by Ranson and coworkers (1935) and Kabat and coworkers (1935). The evidence for descending pathways from the hypothalamus has been reviewed by Magoun (1940). With few exceptions, the functional measurement made in these studies was of mean blood pressure In most cases, no mention was made of heart rate, or the reported changes were of small magnitude Manning and Peiss (1960) demonstrated the variety of sympathetic responses that can be elicited from the hypothalamus

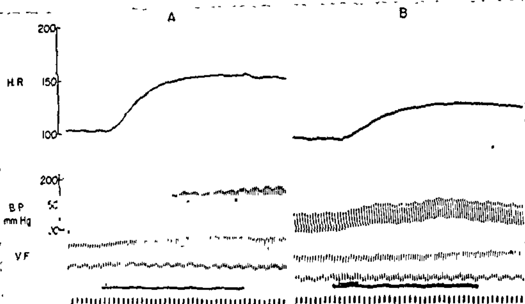


Fig. 2-110 Effect of pentobarbital on heart rate (H.R.), blood pressure (B.P.), and ventricular contractile force (V.F.) in a dog under light chloralose anesthesia A Control response to stimulation of hypothalamus B Restimulation of same point after intravenous administration of 3.5 mg/kg sodium pentobarbital.

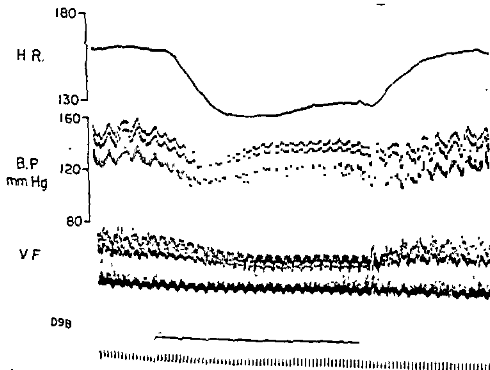


Fig 2-111. Hypothalamic inhibition of heart rate (H R), blood pressure (B P), and ventricular contractile force (V F) in a vagotomized dog under chloralose anesthesia

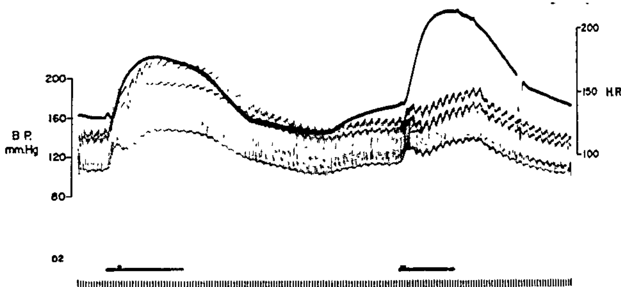


Fig. 2-109. Effects of stimulation of right and left sides of posterior hypothalamus in a dog First stimulus results in moderate accelerator and large augmenter response from left side of hypothalamus Second stimulus results in large accelerator and negligible augmenter response from right side of hypothalamus

2-109 illustrates the comparative effects of stimulation of the right and left sides of the hypothalamus in a dog Two electrodes were positioned 5 mm to the left and right of midline, respectively, in the most caudal part of the hypothalamus The first stimulus shown in the figure was delivered to the left side It resulted in a 38 per cent increase in heart rate and a 95 per cent increase in pulse pressure, indicating significant augmenter activation The second stimulus was delivered to the right side and resulted in a 62 per cent increase in heart rate, with a negligible increase in pulse pressure, indicating a primary activation of sympathetic outflow terminating at or near the cardiac pacemaker This unequal distribution of central representation of accelerator and augmenter pathways was not found in the hypothalamus of the cat

It is possible, therefore, that there is an unequal decussation at some lower level in the brain stem or spinal cord of the cat. It is equally possible that the right and left sympathetic trunks of the cat do not show unequal distribution of accelerator and augmenter fibers The analysis of the cat's sympathetic outflow relative to this point has not been made.

It has already been mentioned that pentobarbital has a depressant effect on the excitability of hypothalamic areas involved in cardiovascular activity. This point requires further emphasis, since it bears on the general problem of anesthesia and drug effects in the investigation of the central nervous integration of the cardiovascular system. The medulla and hypothalamus, two areas that have been most intensively investigated, have differential responses to agents commonly used for the anesthetization and immobilization of experimental animals.

Figure 2-110 illustrates the effects of pentobarbital on the cardiovascular responses to stimulation of the hypothalamus. A is the control response of a cat under light chloralose anesthesia B shows the response to the same stimulus applied to the same point in the hypothalamus 3 min after the intravenous injection of 3 5 mg/kg pentobarbital The recordings indicate that the cardiac components of the response are dramatically reduced, with some persistence of the rise in diastolic pressure. Hypothalamic responses similar to those shown in A of Fig 2-110 cannot be elicited in animals under full anesthetic doses of pentobarbital With high-intensity stimulation, it is possible to produce modest vasoconstrictor responses with blood pressure increases up to 50 mm Hg but no augmenter or accelerator effects. On the contrary, large vasoconstrictor responses are readily elicited from the medulla under pentobarbital anesthesia These two areas also respond differently to *d*-tubocurarine In this case medullary excitability is depressed, including vasomotor and vagal discharge, while hypothalamic excitability is relatively unaffected at dosages that do not produce ganglionic blockade (Peiss et al, 1959).

periments in animals with chloralose anesthesia are also obtained in unanesthetized dogs with chronically implanted electrodes (Rushmer et al, 1959). Moreover, small hypothalamic lesions in these animals significantly reduce the cardiac responses to exercise (Smith et al, 1960). The latter is an important finding, since it confirms that regulation of sympathetic outflow to the heart in an intact conscious animal is mediated by cells in the hypothalamus or by pathways passing through discrete areas of the hypothalamus. This confirms the conclusion reached by Peiss (1960) that in anesthetized animals, integration of the majority of cardiac sympathetic outflow is achieved at levels of the central nervous system above the medulla oblongata.

Additional evidence can be brought to bear on this important point. It has been shown recently (Sarnoff et al, 1960) that the force of atrial contraction can be augmented by a decrease in carotid sinus pressure. Unpublished work by the authors of this section indicates that *this augmentation of myocardial contractility is largely eliminated by midbrain transection*, suggesting that the reflex requires mediation at some higher level of the central nervous system. It appears, therefore, that either afferent fibers from the carotid sinus send off collaterals in the brain stem which ascend to higher levels, or interneurons pass rostrally from the site of medullary input of the carotid sinus nerve. It has been shown that in man stimulation of the carotid sinus nerve reduces the pulse pressure (Carlsten et al., 1958) and that direct application of procaine to the carotid sinus results in an increased pulse pressure (Kezdi, 1953). Both findings are consistent with the conclusion that the degree of activity in the carotid sinus nerve affects the augmenter outflow to the cardiac muscle fibers.

The significance of hypothalamic or suprahypothalamic structures in the regulation of blood pressure and cardiac function is also shown in the chronic experiments in animals with diencephalic lesions (Keller, 1960). A persistent reduction in blood pressure occurred in a large majority of animals with near-total hypothalectomy or prechiasmal ablation, and in a smaller percentage of animals with posterior hypothalectomy. In the first two categories, the experimental data indicate a significant reduction in pulse pressure, which would be consistent with the interpretation that these lesions have interrupted augmenter pathways to the heart. This is further evidence that the carotid sinus reflex and the vasomotor centers in the medulla, which are intact in these animals, are not able to modify reflexly the cardiac sympathetic outflow to any large extent in the absence of certain hypothalamic structures. It is surprising, in fact, that the intact medullary vasomotor apparatus does not compensate for the fall in blood pressure in these animals. This may well indicate *a significant role for supramedullary areas of the central nervous system in the regulation of peripheral vascular tone and in blood pressure homeostasis*.

From this mass of evidence, collected in diverse kinds of experiments, comes the conclusion that the medullary vasomotor center mediates a small part of the total cardiac outflow. Following midbrain transection, for example, stimulation of the dorsal medulla results in relatively small changes in cardiac function. However, stimulation of the ventrolateral medulla produces significant cardiac responses, presumably by activation of efferent pathways from more rostral parts of the brain. It is, therefore, unwarranted to assume that all cardiac outflow, or even a significant part of it, is finally mediated in the vasomotor center of the medulla oblongata. However, this is precisely the generally accepted view, which treats the cells of the vasomotor center as the final common pathway for sympathetic outflow to the cardiovascular system. In this view, the postganglionic discharge to the heart and blood vessels is basically a function of the activity of the medullary cells, and this state of activity is the resultant of their chemical environment, their afferent input from the periphery, and their input from higher levels of the central nervous system.

PROPOSED CONCEPT OF CENTRAL NERVOUS CONTROL OF THE HEART

It is not possible to formulate a specific representation of the central nervous control of the heart without significant advances in knowledge of the anatomic substrates, their interconnections, and their specific effector function. It seems reasonable to expect that any such formulation must eventually be

It is apparent from these and other data that nervous control of cardiovascular activity is seriously modified, both qualitatively and quantitatively, by many commonly used anesthetic agents. Any conclusions regarding central mechanisms must always be subject to the possible modifications introduced by these agents.

Another frequent response to stimulation in the hypothalamus is inhibition of sympathetic outflow to the heart. Folkow et al. (1959) demonstrated the existence in the anterior hypothalamus of the cat of a sharply delimited sympathetic inhibitory area, which is located just ventral to the anterior commissure, and which corresponds closely with the location of the previously described heat-loss area (Magoun et al., 1938). Sympathetic inhibitory responses can be elicited by stimulation of more diffuse areas in the dog brain, including much of the anterior hypothalamus, parts of the limbic system, and the posterior hypothalamus, the latter presumably by activation of pathways descending from more rostral levels This point, however, is not firmly established.

Figure 2-111 shows the results of stimulation of the preoptic region in the same dog from which the huge excitatory response shown in Fig 2-108 was obtained The main effects of stimulation are a prompt reduction in heart rate and in myocardial contractile force. In other dogs, stimulation of this part of the hypothalamus resulted in a fall in blood pressure, with an increased pulse pressure and no change in heart rate or contractile force.

From the variety of responses obtained, it can be concluded that there are cells, fibers, or both in the hypothalamus whose activation results in a direct neural inhibition of sympathetic discharge to blood vessels, the cardiac pacemaker, and the cardiac muscle fibers In this respect, then, there is similarity in the motor outflow to both cardiac and skeletal muscle, in that both effector systems have facilitatory and inhibitory representation in the central nervous system.

Beattie and associates (1930) reported that stimulation of areas in the hypothalamus resulted in cardiac arrhythmias. More recently Purpura and coworkers (1958) have shown similar results from stimulation in the diencephalon and brain stem, and have reported that these cardiac irregularities can be prevented by a variety of pharmacologic agents including the barbiturates. Fuster and collaborators (1960) have correlated specific changes in the ECG with the area of the diencephalon from which they can be induced. The author also observed electrocardiographic changes from stimulation of the brain stem, diencephalon, and limbic system. It is questionable whether the majority of these changes are regulatory in nature, apart from the sinus tachycardia and increased conduction velocity of the cardiac impulse. It has yet to be demonstrated whether most of these electrocardiographic changes occur in normal reflex activity of the sympathetic outflow to the heart. It would be reasonable to expect that a massive sympathetic discharge (e.g., strong emotional stress) may produce changes similar to those reported from stimulation in the central nervous system. It is also possible that the activation of sympathetic outflow by electrical stimulation could produce a pattern of sympathetic discharge that would not be reproduced by physiologic activation. It seems judicious for the present to consider all changes other than sinus tachycardia and increased conduction velocity as having no regulatory function. It is most likely that many of these electrocardiographic changes are incidental resultants of the liberation of norepinephrine at the endings of sympathetic postganglionic fibers evoking augmenter and accelerator responses in the heart.

The above evidence summarizes some of the recent findings relative to elicitation of specific cardiac functional responses by electrical stimulation in several parts of the central nervous system. A survey of the literature reveals a large number of studies involving almost all parts of the brain in relation to the cardiovascular system, including the cerebral cortex, limbic system, subthalamus, and thalamus While it is true that most of these investigations dealt mainly with pressor and depressor responses, it is reasonable to assume that many of these responses involved cardiac mechanisms as well as peripheral vasomotor mechanisms. Much of the literature in this field has been discussed in various reviews (Folkow, 1956a, Ingram, 1960, Uvnäs, 1960, Peiss, 1961). It has been shown that cardiac responses to electrical stimulation in acute ex-

periments in animals with chloralose anesthesia are also obtained in unanesthetized dogs with chronically implanted electrodes (Rushmer et al, 1959). Moreover, small hypothalamic lesions in these animals significantly reduce the cardiac responses to exercise (Smith et al, 1960). The latter is an important finding, since it confirms that regulation of sympathetic outflow to the heart in an intact conscious animal is mediated by cells in the hypothalamus or by pathways passing through discrete areas of the hypothalamus This confirms the conclusion reached by Peiss (1960) that in anesthetized animals, integration of the majority of cardiac sympathetic outflow is achieved at levels of the central nervous system above the medulla oblongata.

Additional evidence can be brought to bear on this important point It has been shown recently (Sarnoff et al, 1960) that the force of atrial contraction can be augmented by a decrease in carotid sinus pressure Unpublished work by the authors of this section indicates that *this augmentation of myocardial contractility is largely eliminated by midbrain transection*, suggesting that the reflex requires mediation at some higher level of the central nervous system. It appears, therefore, that either afferent fibers from the carotid sinus send off collaterals in the brain stem which ascend to higher levels, or interneurons pass rostrally from the site of medullary input of the carotid sinus nerve It has been shown that in man stimulation of the carotid sinus nerve reduces the pulse pressure (Carlsten et al, 1958) and that direct application of procaine to the carotid sinus results in an increased pulse pressure (Kezdi, 1953) Both findings are consistent with the conclusion that the degree of activity in the carotid sinus nerve affects the augmenter outflow to the cardiac muscle fibers

The significance of hypothalamic or suprahypothalamic structures in the regulation of blood pressure and cardiac function is also shown in the chronic experiments in animals with diencephalic lesions (Keller, 1960). A persistent reduction in blood pressure occurred in a large majority of animals with near-total hypothalectomy or prechiasmal ablation, and in a smaller percentage of animals with posterior hypothalectomy. In the first two categories, the experimental data indicate a significant reduction in pulse pressure, which would be consistent with the interpretation that these lesions have interrupted augmenter pathways to the heart. This is further evidence that the carotid sinus reflex and the vasomotor centers in the medulla, which are intact in these animals, are not able to modify reflexly the cardiac sympathetic outflow to any large extent in the absence of certain hypothalamic structures. It is surprising, in fact, that the intact medullary vasomotor apparatus does not compensate for the fall in blood pressure in these animals. This may well indicate *a significant role for supramedullary areas of the central nervous system in the regulation of peripheral vascular tone and in blood pressure homeostasis.*

From this mass of evidence, collected in diverse kinds of experiments, comes the conclusion that the medullary vasomotor center mediates a small part of the total cardiac outflow. Following midbrain transection, for example, stimulation of the dorsal medulla results in relatively small changes in cardiac function. However, stimulation of the ventrolateral medulla produces significant cardiac responses, presumably by activation of efferent pathways from more rostral parts of the brain It is, therefore, unwarranted to assume that all cardiac outflow, or even a significant part of it, is finally mediated in the vasomotor center of the medulla oblongata However, this is precisely the generally accepted view, which treats the cells of the vasomotor center as the final common pathway for sympathetic outflow to the cardiovascular system In this view, the postganglionic discharge to the heart and blood vessels is basically a function of the activity of the medullary cells, and this state of activity is the resultant of their chemical environment, their afferent input from the periphery, and their input from higher levels of the central nervous system

PROPOSED CONCEPT OF CENTRAL NERVOUS CONTROL OF THE HEART

It is not possible to formulate a specific representation of the central nervous control of the heart *without* significant advances in knowledge of the anatomic substrates, their interconnections, and their specific effector *function* It seems reasonable to expect that any such formulation must eventually be

compatible with a more comprehensive concept of autonomic representation in general, and, indeed, of the entire integrative function of the brain. On the other hand, a working hypothesis for cardiac control can serve useful purposes: (1) it can direct the emphasis of our thinking away from presently untenable concepts; (2) it can aid in the design of experimental procedures related to testing specific parts of the hypothesis; (3) it can serve as a model which can be continuously modified, or even wholly discarded, as it is evaluated on the basis of future experimental evidence. In the words of Claude Bernard (1849), "Even mistaken hypotheses and theories are of use in leading to discoveries . . . it seems, indeed, a necessary weakness of our mind to reach truth only across a multitude of errors and obstacles."

Figure 2-112 represents a working hypothesis for the central nervous control of the heart. It essentially provides an afferent input broadly distributed to all levels of the central nervous system. This would include receptors whose afferent input is commonly accepted as subserving cardiac functions, such as certain cutaneous receptors, as well as chemoreceptors, pressoreceptors, and other visceroreceptors. In addition, it is obvious that a wide variety of other sensory information eventually makes connection with effectors subserving cardiovascular responses. Many of these, it is true, may operate indirectly through conditioned

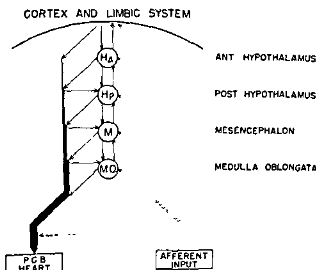


Fig. 2-112. Schematic diagram of proposed concept for central nervous control of the heart. P.C.B.—Heart represents preganglionic cell bodies in intermediolateral cell column whose outflow eventually terminates in the heart.

reflexes or after extensive relay through association areas of the brain. In any event, they eventually terminate on cells whose activity has a direct influence on the cardiovascular system. In this broad view, then, it is likely that potential pathways exist and that they can be activated under certain conditions by almost all types of sensory input.

Integrative functions are accomplished at multiple levels from the spinal cord on up, but for convenience, the system may be divided into two major components. The first comprises the cells and interneurons connecting all intracranial levels. In the figure, five possible levels have been included as examples, viz., medulla oblongata (*M.O.*), *mesencephalon* (*M*), *posterior hypothalamus* (*Hp*), anterior hypothalamus (*Ha*), and the combined cerebral cortex and limbic system. The activity of any level subserving integrative functions for the cardiovascular apparatus will be the net resultant of the total number of cells representing a particular functional response, the chemical environment of these cells, and the temporal and spatial summation of all synaptic connections, including direct afferent input, connections from higher and/or lower integrative areas, as well as feed-back loops. Thus, in the diagram of Fig. 2-112, one must consider that each of the individual connections shown represents both excitatory and inhibitory connections and may therefore represent both positive and negative feedback into the integrative system. The specific activity of each level, of course, will be largely determined by the extent of its afferent input. For example, one would expect a relatively high contribution to the over-all response of the system from the *hypothalamus under* conditions of thermal stress. In similar fashion the relative contribution of cortical and limbic areas to the over-all activity of the integrative apparatus may well be the preponderant factor in determining the cardiovascular response to emotional stress.

By extending Olszewski's (1958) concept of the reticular formation as a central internuncial system to include the entire intracranial apparatus shown in Fig. 2-112, this integrative complex may be viewed as the cardiovascular representation of a central internuncial system.

The schema in Fig. 2-112 provides a *multilevel* efferent outflow from all parts of the central internuncial apparatus, terminating in the second major component of the integrative mechanism, the sympathetic preganglionic cells in the spinal cord. The role of the spinal cord in the integration of cardiovascular activity has been relegated to a *position of secondary importance*.

A large amount of evidence indicates that autonomic outflow from various levels of the

central nervous system may bypass the medullary vasomotor area and pass down the brain stem to the spinal cord (Peiss, 1962). It seems, therefore, that the *sympathetic* preganglionic cells serve as the final common pathway, and finally integrate the total excitatory and inhibitory discharge of the central internuncial system and of the direct intraspinal connections The significance of spinal mediation of cardiovascular reflexes is shown dramatically by Sherrington (1906). The functional responses of the heart to neural influences are basically determined by the discharge rate of the sympathetic preganglionic cells, which are dynamically integrating the total information reaching them from all parts of the nervous system With this arrangement, specific functional response may be triggered by a change in activity arising from any level *of the central* internuncial system or from spinal connections, acting either alone or *in concert* These preganglionic cells represent *the last part* of the central nervous system at which the multiplicity of synaptic functions can be *integrated in* a major fashion, since the bulk of *evidence indicates* that from this point on the activity of these cells represents only *excitatory discharge to* the effector organs The peripheral ganglion cells seem chiefly to provide a mechanism for divergence *and convergence* of these excitatory discharges.

This concept attempts to provide a comprehensive neural organization that can embrace the complex interaction of all factors that contribute to the regulation of cardiac function. It may be far more complex than the actual regulation requires. It may be far too simple, but it provides a general concept of a potential integrative mechanism that is consistent with present knowledge. Future progress will require intensive investigation of the specific role of each level of the central nervous system as it is directly related to cardiovascular representation, and as it is affected by activation of the organism which may be primarily directed toward complex behavioral responses requiring secondary cardiovascular regulation. A system of this general type must finally determine the central nervous outflow to the sympathetic preganglionic cells The amount and distribution of this outflow in turn determine the functional responses of the heart. In this area, recent work has contributed important new information to our understanding of the effector responses of the heart when its sympathetic outflow is activated. This work will be discussed in the following section

PERIPHERAL MECHANISMS

THE EFFERENT CARDIAC NERVES

The *efferent links* in the nervous control of the heart consist of *sympathetic adrenergic fibers* and *vagal cholinergic fibers* Direct nervous control of the effector cells permits *prompt and* sometimes specialized *adjustments* in cardiac *action*, and there is accumulating evidence that this nervous mechanism exercises a *greater* control than either hormonal (adrenal medulla) or inherent *muscular responses* (*length*-tension relationships)

In the dog, sympathetic preganglionic fibers leave the spinal cord by the second, third, and fourth (and *occasionally the first and fifth*) thoracic anterior roots (Fig *2-113*) and pass by way of *the stellate* ganglion to the heart (Randall et al, 1957) Direct electrical stimulation of these roots elicits *remarkable* alterations in arterial blood *pressure, with* significantly greater elevation in *systolic than in* diastolic pressure In the absence of significant changes in vascular distensibility, such responses are best explained on a basis of increased systolic ejection resulting from augmented myocardial contraction Some fibers may pass directly from the upper thoracic ganglia to the heart, but compared with the stellate supply, these are of lesser significance. In man, the cardiac branches of the sympathetic nerves travel to the heart from the *ansa* subclavia and cervical sympathetic nerve *in* superior, middle, and inferior nerve trunks. These pass into the cardiac plexus, *from* whence they reach the coronary vessels and the nodal, conductile, and contractile tissues (Woollard, 1926, Nonidez, 1939, Tcheng, 1951).

The vagal and sympathetic cardiac *nerves* enter *the* cardiac plexus situated over the base of the heart and the great blood *vessels Here* the nerves lose their individual identity, and

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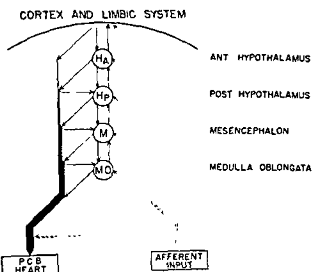


Fig. 2-112. Schematic diagram of proposed concept for central nervous control of the heart. P.C B — Heart represents preganglionic cell bodies in intermediolateral cell column whose outflow eventually terminates in the heart.

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lecture, Starling stated that "the adaptation of the heart to variations *in demand* upon it occurs equally well after total destruction of the nerves connecting the heart with the central nervous system" This statement was interpreted to indicate that the principal mechanisms regulating ventricular *stroke* volume under all circumstances depended upon the degree of diastolic distention That is, the force of myocardial contraction was primarily dependent upon the resting length of the *myocardial fibers* *Only* within recent years has the consensus of opinion returned to the idea that *the nervous system directly influences myocardial metabolism and contractility, and indeed may be powerful enough to override the length-tension mechanism.* Normal ventricular function curves have been shown to differ from classically pictured curves in that they show little or no descending limb (Sarnoff et al, 1954a). A family of curves more accurately describes the relationships within the ventricle with alteration in circulatory state (Sarnoff, 1955).

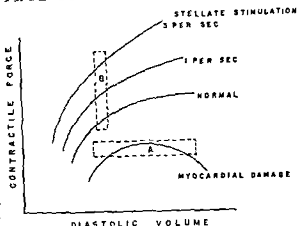


Fig. 2-114. A family of ventricular function curves showing the classical Starling curve (A) in a heart-lung preparation, and a group of three curves (B) showing *the response to sympathetic activation.*

Figure 2-114 shows curves drawn to represent the normal heart, the failing heart, and the heart *during sympathetic stimulation A descending* limb (decreasing force with increasing diastolic volume) does not occur in the normal heart, but *does appear when the myocardium is* damaged or the pericardium removed. The entire curve is also shifted to a lower level. Administration of epinephrine or electrical stimulation of the stellate ganglia at different frequencies systematically shifts the curve upward and to the left, indicating *increased* work per unit of filling pressure (Sarnoff et al, 1960) Thus, in contrast to a continuous traverse along a single curve (Fig. 2-114A), there is, during sympathetic excitation, a traverse from curve to curve with little change in diastolic volume (Fig. 2-114B).

Heart rate is normally established by the periodic discharge of excitatory impulses from the sinoatrial (SA) node, which in turn is continuously influenced by both sympathetic and parasympathetic nerve fibers, which are profusely distributed to it Its rate of discharge may be increased by either increased impulses in the sympathetic nerves or decreased impulses in the parasympathetic nerves If both vagal and sympathetic nerves are cut, the heart generally experiences a moderate acceleration, suggesting that vagal effects predominate. Changes in heart rate under normal conditions involve adjustment of the balance between these two nerve supplies.

The rise in arterial pressure following vagal section is generally explained in terms of associated cardiac acceleration. That vagal section also elicits increased force of contraction was noted by Claude Bernard (1849), but this result is rarely discussed in modern description of the cardiac innervation. While recording intraventricular pressures during vagal section, the author has repeatedly observed significant elevations in ventricular systolic and mean arterial pressure, *with or without* alterations in heart rate Since there is little evidence for direct vagal innervation of the ventricles, this is probably not due to release from inhibitory influences, but rather to *reflex activation of the cardiac sympathetic nerves by mechanical stimulation of vagal afferent fibers* Peiss (1958) has shown that these fibers may exercise powerful influences on the cardiovascular system.

It has been known for over a hundred years that direct electrical stimulation of the sympathetic cardiac nerves results in marked acceleration as well as increased force or vigor of contraction However, kymograph tracings from mercury manometers during such stimulations generally showed a rise in mean pressure, increased heart rate, and an apparent *reduction in amplitude* of pulse oscillation. These observations were undoubtedly responsible for the designation of the cardiac sym-

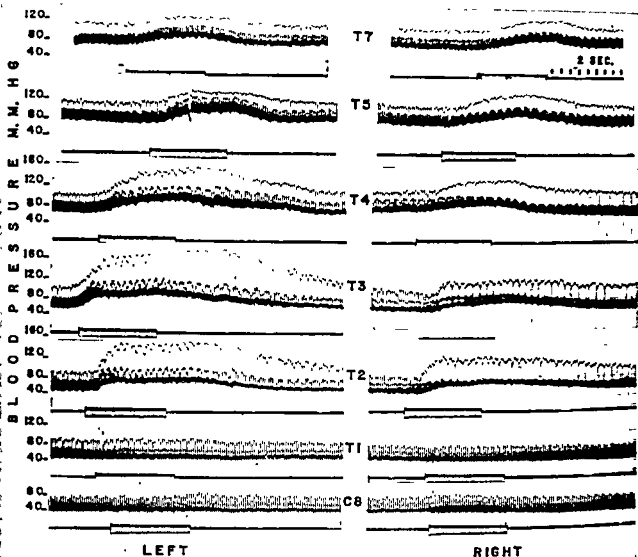


Fig. 2-113. Arterial pressure changes during electrical stimulation of the anterior roots of the thoracic spinal nerves in the dog. Note the augmenter responses during stimulation of the left roots and accelerator responses during stimulation of the right roots. (*From Randall et al, Am. J. Physiol*, 1957.)

it becomes almost impossible to differentiate them within the muscular substance of the various chambers of the heart. Woollard (1926) found that stellectomy resulted in more marked nerve fiber degeneration in the ventricles than in the atria, and that the intramuscular ventricular plexus almost entirely disappeared. *He concluded that the ventricles are innervated chiefly from sympathetic sources and that the atria and the nodal system are innervated by both the sympathetic and parasympathetic systems.* This concept of parasympathetic limitation to the atria and nodal system is generally accepted.

The results of direct electrical stimulation of the cardiac nerves are well known Vagal stimulation slows the heart, decreases the force of atrial contraction, and generally causes elevated mean atrial pressure. It does not directly modify ventricular contractility (Schreiner et al., 1957; Sarnoff et al, 1960). These functional experiments confirm early anatomic studies in which vagal fibers could not be traced to the ventricles (Nonidez, 1939, Cullis et al, 1913), but are contrary to a report by Wang et al. (1960) that *the vagus does depress ventricular contractility.*

DIRECT NERVOUS CONTROL OF CARDIAC ACTION

The enunciation of the "law of the heart" by Starling (1918) altered functional concepts of the relative importance of neural control of heart rate and stroke volume. In his

mals, the chronotropic action of the left stellate and the inotropic action of the right stellate were marked. During the past few years, therefore, investigators have reestablished the use of the descriptive term "augmenter action" of the cardiac sympathetic nerves. *Indeed, in many instances augmentation is recognized as more significant than acceleration.* In order to be certain that elevations in arterial and ventricular pressures originated in stronger myocardial contraction, experiments were carried out in which the heart was tightly clamped between the atria and ventricles. Blood could neither enter the ventricles from the atria nor leave by way of the large arteries. Pressure promptly became elevated in such an isovolumetric ventricle when the clamp was applied, but when stimulation of the sympathetic nerves was superimposed, pressures in both ventricles rose remarkably higher, indicating a great increase in myocardial contractile tension (Kelso et al., 1959, Anzola et al., 1956).

ALTERATIONS IN CARDIODYNAMICS DURING SYMPATHETIC NERVE STIMULATION

Until recently, ventricular emptying was believed to be almost complete, with very little blood remaining in the chamber at the conclusion of systole. Simultaneous cardiometer and arterial blood pressure tracings illustrate the close correlation between increased arterial pulse pressure and *systolic ejection* during stellate stimulation (Fig. 2-116A). There was frequently little or no alteration in the diastolic volume of the ventricles. Fast *tracings* revealed a marked sharpening of systolic upstroke in the pressure pulse and a steeper systolic gradient with a smaller end-systolic volume in the cardiometer trace during activation of the sympathetic nerves (Fig. 2-116B). Thus, it is clear that the left ventricle is more completely emptied into the aorta and the large central arteries, resulting in a significantly augmented arterial pulse. Increases of as much as 80 to 100 mm Hg in the pressure

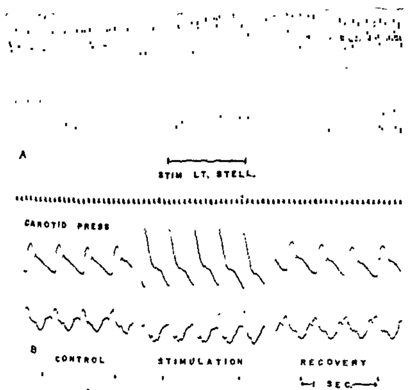


Fig. 2-116. Simultaneous recordings of carotid pressure (top tracing in each pair) and cardiometer changes during electrical stimulation of the cardiac sympathetic nerves. In the cardiometer tracing, systolic emptying is indicated by a downstroke of the optical beam.

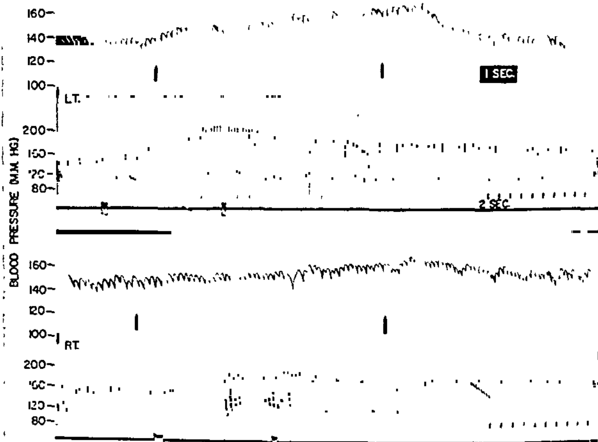


Fig. 2-115. Simultaneous recordings of arterial pressure responses to stellate stimulation by the traditional mercury manometer–smoked kymograph and the electromanometer–Sanborn Polyviso Note that the speed of the smoked kymograph was faster than that of the Polyviso, but signals indicate simultaneous points

pathetic nerves as the *accelerator nerves*, and the continued use of the term perpetuates the concept that acceleration is their most important (or even their sole) function. Rushmer et al (1959) have shown that in nonanesthetized dogs, tachycardia is the primary response in moderate exercise However, *these experiments reveal increased cardiac output with little change in ventricular dimensions. At elevated blood pressures, the heart mobilizes more energy in the performance of work* This is a form of augmentation Without this sympathetic effect, the heart would of necessity dilate along a Starling curve. With the development of more adequate recording equipment, a significant alteration in arterial pulse pressure became evident (Fig 2-115). A large elevation in systolic pressure with little change in diastolic pressure indicated a marked influence of the sympathetic cardiac nerves on the volume of systolic ejection. This alteration in cardiac hemodynamics cannot be recorded by the older (smoked drum-kymograph-mercury manometer) techniques, and therefore an erroneous interpretation of the relative significance of the chronotropic and inotropic actions of the cardiac sympathetic nerves was introduced

During stimulation of the stellate ganglia or anterior roots in several hundred experiments on anesthetized open-chest dogs, a consistent difference in response to excitation of the left vs. the right side has emerged (Fig 2-113). In a majority of animals, right-side stimulation elicits a marked chronotropic response with little-to-moderate augmentation in systemic arterial pressure. *In a majority of left-stellate stimulations, a pronounced augmenter action is induced, with little or no change in heart rate* (Randall et al., 1956, Shipley et al, 1945). However, these responses were not invariable, and in some ani-

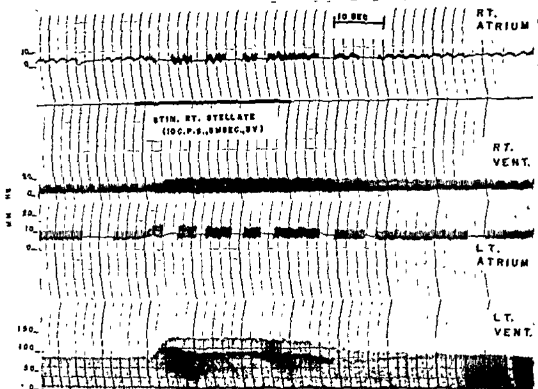


Fig 2-117. Simultaneous recording of pressures from the four chambers of the heart during electrical excitation of the right stellate ganglion Mean pressures were recorded alternately in the atrial traces Both augmentation and acceleration accompanied the stimulation Note the increase in left atrial mean pressure early in the augmenter response

before each ventricular contraction (Linden et al, 1960) More vigorous atrial contraction during sympathetic stimulation resulted in a greater increment in ventricular diastolic pressure

Further examination of Fig 2-117 reveals a definite elevation in left atrial pressure with little change or slight decline in right atrial pressure during stimulation. However, this was not a constant finding, as illustrated in Fig 2-118 In this experiment, both right and left atrial pressures declined significantly during the stimulation The latter response was observed by Sarnoff et al (1960), who reported a marked decline in mean atrial pressures in all their animals They also demonstrated a shift of the ventricular function curves to the left when either left atrial or left ventricular end-diastolic pressure was plotted against stroke work These workers further reported comparable effects of norepinephrine on ventricular function In all experiments, atrial pressure waves were augmented in force by sympathetic stimulation The authors cannot account for this deviation in mean atrial pressure responses in the two series of experiments, or between different animals in this series In some experiments, atrial pressures increased, in others declined, and in still others remained constant The two atrial pressures did not always change in parallel fashion Pulmonary vasomotor action in response to electrical excitation of the thoracic sympathetic outflow to the pulmonary vascular bed was not recorded in either set of experiments De Burgh Daly (1956) has demonstrated active vasomotor control of these vessels, however, and it is conceivable that a variable response in pulmonary vascular resistance could account for the variable changes in mean left atrial pressure.

It is now abundantly clear that stimulation of the sympathetic nerves to the heart profoundly influences cardiac action. Systolic pressures rise much faster and reach higher levels because of the development of much higher myocardial fiber tension The duration of both contraction and isometric relaxation is markedly shortened, resulting in a lengthened period of diastolic filling in those experiments in which heart rate did not change or was held constant by atrial pacing. Even when

pulse have been observed both in animals and in man (Randall et al., 1957, 1960) during thoracic ganglion stimulation.

Optical recording of critically damped pressure pulses from the left ventricle and carotid artery permitted description of characteristic alterations in form and duration of pulses during sympathetic stimulation (Randall et al., 1960). A remarkable acceleration in the rate of pressure rise first appeared in the same cycle in which augmentation in amplitude was detectable. The rate of change progressively increased throughout the early phase of augmentation until it had more than doubled (from slightly less than 1 0 to over 2 0 mm Hg/msec). Systolic rise in pressure was straight throughout most of systole, deviating only after near-peak pressures were attained. Gently rounded summits of control pressure pulses were converted to sharply peaked curves of shorter duration. These alterations in contractility were unrelated to changes in heart rate

In addition to the increased rate of pressure rise during ventricular contraction, steeper slopes during early diastole revealed a more rapid fall in intraventricular pressure This indicates more rapid myocardial relaxation as a result of sympathetic excitation, and undoubtedly plays an important role in the rapid ventricular filling phase of early diastole In some instances ventricular pressures fell slightly below that which obtained at a comparable period in the control pulses

Still another significant change in the ventricular pressure pulse elicited by stellate stimulation was the change in relative durations of systole and diastole.

In a series of pulses in which the total cycle length remained constant at 0 4 sec, systole decreased from 0 20 sec to a minimum duration of 0 14 sec The period of active relaxation decreased moderately, while total diastole increased from 0.20 to 0 26 sec. Thus, there was a marked decrease in duration of systole, during which pressure rose much more rapidly to higher peaks and with ejection of a greater volume of blood The increases in the length of diastole permitted a correspondingly longer time for more complete ventricular relaxation and greater filling. In those instances in which the heart rate accelerated and total cycle time was decreased, there was correspondingly less increase in systolic ejection and in augmentation of the arterial pressure pulse, even though the velocity of contraction and relaxation were increased as much as in those experiments in which no heart rate changes occurred.

The shortening of systole resulting from sympathetic stimulation actually assumes great importance when heart rate accelerates, since it permits considerably more shortening of total cycle time than would otherwise be possible before encroachment upon ventricular filling time becomes critical. This relationship is particularly interesting in that it seems to represent a built-in factor to compensate the otherwise mutually extinguishing phenomena of increased ejection (positive inotropic action) and increased rate (chronotropic action).

The alteration in mechanical events of the cardiac cycle resulting from sympathetic stimulation is associated with altered electrical phenomena such as increased conduction velocity in the atrium, AV node, and the ventricles (Brooks et al, 1955; Hoffman et al., 1959). Both external work and power produced by the contracting heart muscle are greatly influenced by the precise timing of fiber shortening in different parts of the ventricles. Intensified contraction simultaneous with a decreased period of contraction implies more synchronous shortening of the myocardial fibers, and this represents a most significant influence of the sympathetic nerves on cardiac action.

The recording of simultaneous pressures from all four chambers of the heart during electrical stimulation of the sympathetic innervation is illustrated in Fig. 2-117 It is immediately evident that stimulation of one stellate ganglion may exert a profound influence on all four chambers, and this is generally true regardless of whether the right or left stellate is excited. In addition to the remarkable augmentation in ventricular contraction, it is apparent that the a wave of atrial contraction is also strengthened. That it is the a wave and not the c wave has been thoroughly demonstrated by identification with the P wave of the ECG and by direct recording of atrial force by means of a Walton strain gauge arch (Ulmer et al., 1961). The rate of rise of intra-atrial pressure increased and the duration of atrial systole decreased as a result of sympathetic stimulation. Similar observations were reported by Sarnoff et al. (1960), who examined the a wave during sympathetic stimulation in the dog with heart block. Such studies permitted careful examination of atrial responses without the complications of simultaneous ventricular interference. High-speed tracings also revealed a definite increment in left ventricular diastolic pressure as a result of left atrial systole. These data are more readily discernible in the heart block preparation in which several atrial contractions contributed to filling

in concentration of catecholamines in coronary sinus blood during sympathetic stimulation. That the catecholamines will increase the vigor of ventricular contraction has been established for many years. It is also clear that the catecholamines produce a shift of the ventricular function curves to the left (Sarnoff et al., 1960). It is reasonable, therefore, to conclude that direct sympathetic nerve stimulation elicits these responses by the liberation of catecholamines (chiefly norepinephrine) at the postganglionic endings in myocardial tissues. This occurs at sympathetic endings in all parts of the heart, with consequent increased excitability, conduction velocity, and contractility. The result is a more synchronous contraction of individual myocardial units and with it greater work performance

When animals are treated with reserpine, norepinephrine disappears from the heart, and stimulation of the sympathetic nerve no longer accelerates or augments the force of cardiac contraction (Burn et al, 1960) However, if norepinephrine is given by slow infusion, the normal effect of postganglionic stimulation returns These facts are consistent with the view that efferent impulses in the sympathetic nerve liberate norepinephrine from a store, and the effect of a given stimulation depends upon the size of the store.

INTERRELATION BETWEEN DIRECT NERVOUS AND LENGTH-TENSION REGULATION OF THE HEART

Conventional concepts of the reflex function of the carotid sinus hold that it primarily influences heart rate and peripheral resistance (Heymans et al, 1958) Sarnoff and associates (1960) have shown that the carotid sinus can vary the vigor of atrial contraction by reflexly changing both efferent vagal and sympathetic impulses and can thus vary ventricular end-diastolic pressure and fiber length It can also reflexly modify ventricular contractility in such a way that from a given end-diastolic pressure or fiber length with a low carotid pressure, ventricular contraction is augmented, and from a high carotid pressure, it is diminished

Direct anatomic pathways exist whereby the central nervous system may systematically regulate ventricular contraction by either of two ways (1) It can augment atrial contraction by means of the sympathetic system and diminish it via the vagus. Greater or lesser quantities of blood may thus be actively pumped into the ventricles, with consequent alteration in ventricular fiber length and volume of systolic ejection in strict accordance with Starling's law of the heart (2) By way of direct sympathetic innervation of the ventricles, it can augment ventricular contraction from any given end-diastolic position. Such augmented contraction results in more complete systolic emptying, a lower diastolic impedance to ventricular inflow (Buckley et al., 1956), and a relatively greater influence of simultaneously augmented atrial systole

NERVOUS CONTROL OF CORONARY VESSELS

The nerves coursing along coronary vessels are so plentiful that it once appeared that they received the entire cardiac innervation. It is not known, however, how many of these fibers end on the vascular smooth muscle cells. Some evidence indicates that such innervation is very sparse. Stimulation of the stellate ganglia produces an increase in coronary flow even with minimal changes in heart rate, but such stimulation is accompanied by such profound mechanical and metabolic influences that it is presently impossible to judge the extent to which blood flow may be changed by specific vasomotor fibers Evidence for sympathetic vasoconstrictor activity has been obtained in the fibrillating heart, where stellate stimulation generally decreased coronary flow and stellatectomy increased it Katz and coworkers (1939) reported the existence of sympathetic vasoconstrictor fibers However, stimulation of the postganglionic cardiomotor fibers gives rise to increased coronary flow, which is reasonably proportional to increased cardiac activity. Therefore, evidence for coronary vasoconstrictor fibers is not strong

According to some reports, such elevations in coronary flow are not influenced by sympatholytic or parasympatholytic drugs (Juhasz-Nagy et al, 1959) This group has also recently made the surprising suggestion that the sympathetic cardiac nerves in the cat contain preganglionic fibers in addition to the well-recognized postganglionic fibers These fibers are said not to synapse within the stellate ganglion, but to continue on to peripheral synapses within the wall of the heart (Szentivanyi et al, 1956). Electrical stimulation of these fibers is reported to result in coronary

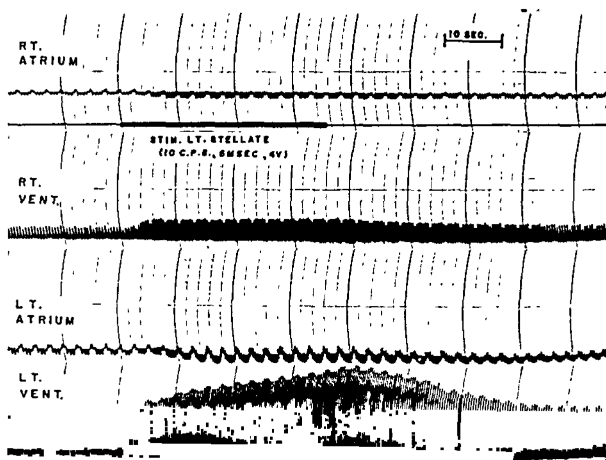


Fig. 2-118. Simultaneous recording of pressures from the four chambers of the heart during left stellate stimulation Note that both right and left atrial mean pressures decline significantly during the stimulation Moderate acceleration accompanied the augmentation and fall in atrial pressures, and all pressures returned to normal promptly upon cessation of stimulation.

heart rate increased, the development of increased myocardial tension was prominent. As a result of these ventricular reactions to sympathetic activation, *systolic emptying was more complete and arterial pressures were significantly elevated.* It is important to realize that *the more forceful contraction from any given* filling pressure does not necessarily involve any change in fiber length at which the contraction starts. The larger stroke volume resulting from more complete systolic emptying places the ventricle on the lower and flatter portion of its pressure-length curve during subsequent diastole Into this more receptive ventricle, blood passes rapidly from the atrium during the period of early filling, and, under the impetus of augmented atrial contraction, additional filling occurs late in diastole. This, coupled with a modest increase in pulmonary artery pressure, associated with augmented right ventricle pressure, *significantly* increases the gradient across the entire pulmonary vascular bed and correspondingly increases the delivery of blood from the large pulmonary blood reservoir to the left side of the heart. Thus, augmented cardiac output and resulting increased arterial pressures may be maintained *for many hours. Such elevated* arterial pressures have, in fact, been maintained for prolonged periods by continuous electrical stimulation of the stellate ganglia at relatively low frequencies (Rohse et al, 1957).

ROLE OF LOCALLY PRODUCED NOREPINEPHRINE IN THE HEART

In tissues innervated by postganglionic sympathetic fibers, norepinephrine is present This was first shown in blood vessels (Schmiterlow, 1948) and then demonstrated in the heart (Goodall, 1951; Burn et al, 1960). Both Outschoorn and coworkers (1952) and Siegel and coworkers (1960) found considerable increase

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constriction or dilatation without changes in other parameters of cardiac function. This group also reported preganglionic "B" fibers in the cardiac sympathetic nerves of the dog; they synapse with intracardiac neurons which are coronary vasomotor fibers. Confirmation of these reports by other workers would radically change present concepts of the terminal innervation apparatus in the heart.

Some investigators have observed decreased coronary flow in the intact heart when they stimulated the vagus nerves, and increased flow following bilateral vagotomy. Others report no change or even opposite results. Folkow (1956) emphatically states that the vagus does not contain vasoconstrictor fibers since acetylcholine in all concentrations markedly dilates the coronary vessels. Thus, there is accumulating evidence that the vagus plays little or no role in the motor innervation of the coronary arteries (Juhasz-Nagy et al., 1959).

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